National Institute for Health and Care Excellence

Draft for consultation

Termination of Pregnancy

[M] Cervical priming before surgical termination of pregnancy

NICE guideline <TBC>

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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ISBN:

Contents

Cervical priming before surgical termination of pregnancy

This evidence report contains information on 2 reviews relating to cervical priming before surgical termination of pregnancy.

- What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation?
- What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

Cervical priming up to 13^{+6} weeks' gestation?

Review question

What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation?

Introduction

The aim of this review is to determine the optimal cervical priming regimen (if any) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women who are having surgical termination of pregnancy up to and including 13^{+6} weeks' gestation
Intervention	Cervical priming agents: • Mifepristone (oral) • Misoprostol (vaginal, sublingual, buccal)
Comparison	• Cervical priming agent versus placebo or no agent • Cervical priming agent A versus cervical priming agent B • Cervical priming agent A – dose A versus cervical priming agent A – dose B • Cervical priming agent A – interval A versus cervical priming agent A – interval B • Misoprostol route A versus misoprostol route B
Outcome	**Critical outcomes:** • Incomplete abortion (need for re-evacuation or re-aspiration) • Cervical trauma • Uterine perforation **Important outcomes:** • Ease of cervical dilation/force required to dilate (e.g., measured by tonometer) • Pre-operative pain using patient reported pain score/validated pain scales • Pre-operative expulsion of fetus • Pre-operative bleeding

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

Only studies conducted from 2000 were considered for this review question, as the first RCOG guidance on termination of pregnancy was published in 2000 and was followed by substantial changes in practice.

Eighteen randomised controlled trials (RCTs; number of participants, N=8,538) were included in the review (Ashok 2000; Cakir 2005; Chitaishvili 2007; Carbonell Esteve 2006; de Jonge 2000; Inal 2003; Li 2003; Meirik 2012; Saav 2015; Saxena 2003; Saxena 2006; Saxena 2008; Sharma 2005; Sharma 2011; Tang 2004; Vimala 2003; Vimala 2004a; Vimala 2004b).

Ten RCTs compared a single priming agent (misoprostol) against placebo or no agent (Cakir 2005; Chitaishvili 2007; de Jonge 2000; Inal 2003; Li 2003; Meirik 2012; Saxena 2003; Sharma 2005; Sharma 2011; Vimala 2003. One RCT compared 2 different cervical priming agents (mifepristone against misoprostol; Ashok 2000). One RCT compared 2 different doses of the same cervical priming agent (200micrograms (mcg) sublingual misoprostol against 400mcg sublingual misoprostol; Vimala 2004b). Three RCTs compared different intervals between administration of a cervical priming agent and the termination (mifepristone 24 hours before termination versus mifepristone 48 hours before the termination [n=1; Ashok 2000], sublingual misoprostol 1 hour before the termination versus sublingual misoprostol 3 hours before the termination [n=1; Saav 2015], sublingual misoprostol 2 hours before the termination versus sublingual misoprostol 3 hours before the termination [n=1; Vimala 2004b], vaginal misoprostol 1 hour before the termination versus vaginal misoprostol 3 hours before the termination [n=1; Saav 2015]). Six RCTs compared different routes of administering misoprostol (sublingual misoprostol versus vaginal misoprostol; Carbonell Esteve 2006; Saav 2015; Saxena 2006; Saxena 2008; Tang 2004; Vimala 2004a).

One RCT (Meirik 2012) reported data based on parity and 2 RCTs (Saav 2015; Tang 2004) only included nulliparous women. There was no subgroup data available based on medical conditions, age, or gestational age.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

The original review protocol included oral misoprostol and 2 additional comparisons: 1) a combination of cervical priming agents versus a single cervical priming agent, and 2) a combination of cervical priming agents versus a different combination of cervical priming agents. However, this resulted in the identification of a larger number of studies than was feasible to include within the timeframe for the development of this NICE guideline. The committee agreed that it would be very unlikely that oral misoprostol would be recommended as it is known to have a longer absorption time and greater side effects compared with other routes of misoprostol administration. Therefore, studies with only 2 arms were excluded if 1 of them used oral misoprostol as the cervical priming agent; and outcome data for oral misoprostol arms were not extracted for studies with greater than 2 arms. This resulted in the exclusion of 13 studies. Similarly, the committee agreed that studies including combinations of priming agents could be excluded as more than 1 priming agent was unlikely to be required in this population due to the low gestational age; however, no studies were excluded for this reason.

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Ashok 2000 RCT UK	n=90 Women aged 15 to 40 requesting surgical termination of pregnancy 6.6 to 12.1 weeks' gestation	**24 hour mifepristone:** 200mg oral mifepristone 24 hours before termination **48 hour mifepristone:** 200mg oral mifepristone 48 hours before termination	• Cumulative force required to dilate cervix • Pre-operative pain • Pre-operative bleeding	
Cakir 2005 RCT Turkey	N=160 (including n=40 oral misoprostol and n=40 oral placebo not of interest for this review) Women requesting termination of pregnancy 7 to 10 weeks' gestation	**Vaginal misoprostol:** 400micrograms (mcg) vaginal misoprostol 3 hours before termination **Vaginal placebo:** placebo (agent not reported) 3 hours before termination	• Pre-operative pain • Pre-operative expulsion • Pre-operative bleeding	
Carbonell Esteve 2006 RCT Spain	N=1,430 Women requesting surgical termination and willing to abstain from intercourse for 14 days following termination ≤84 days gestation	**Sublingual misoprostol:** 400mcg sublingual misoprostol 1 to 3 hours before termination **Vaginal misoprostol:** 400mcg vaginal misoprostol 1 to 3 hours before termination	• Cervical trauma • Uterine perforation • Ease of cervical dilation	
Chitaishvili 2007 RCT Georgia	N=349 Healthy women requesting termination 8 to 12 weeks' gestation	**Sublingual misoprostol:** 400mcg sublingual misoprostol 1 hour before termination **Sublingual placebo:** placebo (agent not reported) 1 hour before termination	• Pre-operative pain • Pre-operative bleeding	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
de Jonge 2000 RCT South Africa	N=278 Women requesting termination <13 weeks' gestation	**Vaginal misoprostol:** 600mcg vaginal misoprostol 2 to 3 hours before termination **Placebo:** 750mg ascorbic acid 2 to 3 hours before termination	• Incomplete abortion • Pre-operative pain	
Inal 2003 RCT Turkey	N=120 (including n=30 oral misoprostol and n=30 oral placebo not of interest for this review) Inclusion criteria not reported	**Vaginal misoprostol:** 200mcg vaginal misoprostol 10 hours before termination **Vaginal placebo:** placebo (agent not reported) 10 hours before termination	• Pre-operative bleeding	
Li 2003 RCT China	N=126 Healthy women requesting a surgical termination under general anaesthesia 9 to 12 weeks' gestation	**Vaginal misoprostol:** 400mcg vaginal misoprostol 4 to 6 hours before termination **Vaginal placebo:** placebo (agent not reported) 4 to 6 hours before termination	• Cumulative force required to dilate cervix • Pre-operative pain • Pre-operative bleeding	
Meirik 2012 RCT International	N=4,972 Women requesting termination ≤11^{+1} weeks' gestation	**Vaginal misoprostol:** 400mcg vaginal misoprostol 3 hours before termination **Vaginal placebo:** placebo (agent not reported) 3 hours before termination	• Incomplete abortion • Cervical trauma • Uterine perforation • Pre-operative pain • Pre-operative bleeding	
Saav 2015 RCT Sweden	N=184 Healthy nulliparous women requesting surgical termination of pregnancy	**1hr sublingual misoprostol:** 400mcg sublingual misoprostol and vaginal placebo (agent not reported) 1 hour	• Cervical trauma • Uterine perforation • Force required to dilate cervix • Pre-operative pain	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	6 to 13 weeks	before termination **3hr sublingual misoprostol:** 400mcg sublingual misoprostol and vaginal placebo (agent not reported) 3 hours before termination **1hr vaginal misoprostol:** 400mcg vaginal misoprostol and sublingual placebo (agent not reported) 1 hour before termination **3hr vaginal misoprostol:** 400mcg vaginal misoprostol and sublingual placebo (agent not reported) 3 hours before termination	• Pre-operative expulsion • Pre-operative bleeding	
Saxena 2003 RCT India	N=50 Healthy women requesting termination 6 to 12 weeks' gestation	**Sublingual misoprostol:** 400mcg sublingual misoprostol 3 hours before termination **Control:** no cervical priming given	• Incomplete abortion • Cervical trauma • Uterine perforation	
Saxena 2006 RCT India	N=100 Healthy women requesting termination 6 to 12 weeks	**Sublingual misoprostol:** 400mcg sublingual misoprostol at home 2 hours before termination **Vaginal misoprostol:** 400mcg vaginal misoprostol at	• Pre-operative pain • Pre-operative expulsion • Pre-operative bleeding	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		hospital 2 hours before termination		
Saxena 2008 RCT India	N=200 (including n=50 oral misoprostol not of interest for this review) Healthy women requesting termination of pregnancy 6 to 12 weeks' gestation	**Sublingual misoprostol:** 400mcg sublingual misoprostol at home 2 hours before termination **Vaginal misoprostol:** 400mcg vaginal misoprostol at hospital 2 hours before termination	• Pre-operative pain • Pre-operative expulsion • Pre-operative bleeding	
Sharma 2005 RCT UK	N=90 (including n=30 oral misoprostol not of interest for this review) Women aged 18 or older requesting surgical termination of pregnancy 7 to 10 weeks' gestation	**Vaginal misoprostol:** 800mcg vaginal misoprostol 1 hour before termination **Control:** no cervical priming given	• Cervical trauma • Uterine perforation • Cumulative force required to dilate the cervix • Pre-operative pain • Pre-operative bleeding	Cervical trauma and uterine perforation not directly reported but reported that all women had an 'uncomplicated procedure' (p. 458)
Sharma 2011 RCT India	N=221 Women with gravidity ≤4 requesting termination 5 to 12 weeks' gestation	**Sublingual misoprostol:** 400mcg sublingual misoprostol 3 hours before termination **Control:** no cervical priming given	• Incomplete abortion • Uterine perforation • Pre-operative pain • Pre-operative bleeding	Unclear whether pain and bleeding were pre-operative as timing was not reported
Tang 2004 RCT Hong Kong	N=80 Nulliparous women requesting termination	**Sublingual misoprostol:** 400mcg sublingual misoprostol 3 hours before termination	• Cumulative force required to dilate the cervix • Pre-operative pain • Pre-operative expulsion	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	<12 weeks' gestation	**Vaginal misoprostol:** 400mcg vaginal misoprostol 3 hours before termination	• Pre-operative bleeding	
Vimala 2003 RCT India	N=60 Healthy women requesting surgical termination by vacuum aspiration 6 to 11 weeks' gestation	**Sublingual misoprostol:** 400mcg 2 hours before termination **Sublingual placebo:** 100mg sublingual pyridoxine 2 hours before termination	• Incomplete abortion • Uterine perforation • Pre-operative pain	
Vimala 2004a RCT India	N=100 Women requesting surgical termination by vacuum aspiration 6 to 12 weeks' gestation	**Sublingual misoprostol:** 400mcg sublingual misoprostol 3 hours before termination **Vaginal misoprostol:** 400mcg vaginal misoprostol 2 hours before termination	• Incomplete abortion • Uterine perforation • Pre-operative pain • Pre-operative bleeding	
Vimala 2004b RCT India	N=120 Women requesting termination of pregnancy 6 to 11 weeks' gestation	**2hr 400mcg sublingual misoprostol:** 400mcg sublingual misoprostol 2 hours before termination **3hr 400mcg sublingual misoprostol:** 400mcg sublingual misoprostol 3 hours before termination **2hr 400mcg vaginal misoprostol:** 400mcg vaginal misoprostol 2	• Incomplete abortion • Uterine perforation • Pre-operative pain • Pre-operative expulsion • Pre-operative bleeding	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		hours before termination **3hr 400mcg vaginal misoprostol:** 400mcg vaginal misoprostol 3 hours before termination		

mcg: micrograms; RCT: randomised controlled trial

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Resource impact

Table 3: Unit costs associated with cervical priming before surgical termination

Resource	Unit costs	Source
Hourly Cost Nurse including on costs	£21.56	BPAS Correspondence
Staff cost per additional priming (assume 45 minutes)	£16.17	BPAS Correspondence
Misoprostol 7 microgram per 1 hour	£93.00 per unit	BNF 75
Mifepristone 200mg	£17.55 per unit	BNF 75

All unit costs and cost estimates for staff time presented above are based on costs obtained from correspondence with the British Pregnancy Advisory Service (BPAS). Whilst the BPAS is not a NHS organisation, the majority of terminations of pregnancies carried out at their clinics are NHS funded. The costs therefore may not accurately reflect those to the NHS although should give an estimate of size and magnitude of the above activites. The committee would expect given the economies of scale and specialisation that the BPAS are able to take advantage of in this area that the costs above are likely to be an underestimate of providing these activities in an NHS setting.

The committee highlighted that if cervical priming was to be offered for individuals who are 14^{+0} weeks pregnant there would be an increase in contact time with staff. Therefore there would need to be either an increase in staffing or a reduction in the capacity and number of terminations of pregnancy that could be given. The unit costs above focus on increased staffing given the equity considerations for any NICE recommendation.

Drug costs are taken from the BNF. Again the committee highlighted that the price paid by the BPAS or other similar organisations is likely to be significantly lower especially for misoprostol where an estimated cost of less than £2 per termination of pregnancy was estimated by the BPAS.

Evidence statements

Comparison 1. Misoprostol versus no cervical priming agent (± placebo)

Critical outcomes

Incomplete abortion

RCT evidence showed a lower clinically important difference in the rate of incomplete abortion in the 'misoprostol' group (400-600mcg; 2-3 hours before termination) compared with the 'no cervical priming agent (± placebo)' group in women of mixed parity (5 RCTs, n=5,512; RR=0.44 [95% CI 0.21, 0.9]; very low quality) or parous women (1 RCT, n=2,714; RR=0.18 [95% CI 0.08, 0.44]; high quality). However, RCT evidence did not detect a clinically important difference in the rate of incomplete abortion between the 'misoprostol' group (400mcg; 3 hours before termination) and the 'no cervical priming agent (± placebo)' group in nulliparous women (1 RCT, n=2,144; RR=0.53 [95% CI 0.23, 1.25]; moderate quality); however, there was uncertainty around the estimate.

Cervical trauma

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the 'misoprostol' group (400-800mcg; 1-3 hours before termination) and the 'no cervical priming agent (± placebo)' group in women of mixed parity (3 RCTs, n=5,130; RR=0.25 [95% CI 0.03, 2.23]; very low quality) or parous women (1 RCT, n=2,798; RR=0.20 [95% CI 0.01, 4.17]; low quality); however, there was uncertainty around the estimates. RCT evidence reported no events of cervical trauma in either the 'misoprostol' group or the 'no cervical priming agent (± placebo)' group for nulliparous women (1 RCT, n=2,172; moderate quality); therefore, differences between groups could not be estimated.

Uterine perforation

RCT evidence did not detect a clinically important difference in the rate of uterine perforation between the 'misoprostol' group (400-800mcg; 1-3 hours before termination) and the 'no cervical priming agent (± placebo)' group in women of mixed parity (5 RCTs, n=5,441; RR=1.30 [95% CI 0.49, 3.47]; very low quality) or parous women (1 RCT, n=2,798; RR=3.01 [95% CI 0.31, 28.89]; low quality); however, there was uncertainty around the estimates.

RCT evidence reported no events of uterine perforation in either the 'misoprostol' group or the 'no cervical priming agent (± placebo)' group for nulliparous women (1 RCT, n=2,172; no events observed; moderate quality); therefore, differences between groups could not be estimated.

Important outcomes

Cumulative force required to sufficiently dilate cervix

RCT evidence showed a higher clinically important difference in the force required to dilate the cervix in the 'misoprostol' group (400-800mcg; 1-6 hours before termination) compared with the 'no cervical priming agent (± placebo)' group (2 RCTs, n=143; MD=-7.08N [95% CI -11.67, -2.49]; high quality).

Pre-operative pain

RCT evidence showed a higher clinically important difference in any pre-operative pain in the 'misoprostol' group (400-800mcg; 1-6 hours before termination) compared with the no cervical priming agent (± placebo)' group (7 RCTs, n=5,877; RR=2.37 [95% CI 1.85, 3.04]; very low quality). In contrast, RCT evidence showed a lower clinically important difference in any abdominal pain in the 'misoprostol' group (400mcg; 3 hours before termination) compared with the 'no cervical priming agent (± placebo)' group (1 RCT, n=221; RR=0.37 [95% CI 0.18, 0.78]; low quality); however, it is unclear whether this was pre-operative pain.

RCT evidence did not detect a clinically important difference in mild pre-operative pain (RR=0.90 [95% CI 0.41, 1.99]; low quality) between the 'misoprostol' group (400mcg; 4-6 hours before termination) compared with the 'no cervical priming agent (± placebo)' group (1 RCT, n=84); however, there was uncertainty around the estimate. RCT evidence showed a higher clinically important difference in moderate to severe pre-operative pain (RR=37 [95% CI 2.30, 594.63]; high quality) in the 'misoprostol' group compared with the 'no cervical priming agent (± placebo)' group (1 RCT, n=84).

Pre-operative expulsion

RCT evidence reported no events of pre-operative expulsion in either the 'misoprostol' group (400mcg; 3 hours before termination) or the 'no cervical priming agent (± placebo)' group (1 RCT, n=80; low quality); therefore, differences between groups could not be estimated.

Pre-operative bleeding

RCT evidence showed a higher clinically important difference in any pre-operative bleeding (7 RCTs, n=5,805; RR=5.9 [95% CI 5.08, 6.86]; high quality), mild pre-operative bleeding (1 RCT, n=84; RR=4.50 [95% CI 1.03, 19.60]; moderate quality), moderate to severe pre-operative bleeding (1 RCT, n=84; RR=17 [95% CI 1.01, 285.40]; moderate quality) and pre-operative bleeding measured in ml (1 RCT, n=80; MD=2.90ml [95% CI 2.61, 3.19]; moderate quality) in the 'misoprostol' group (200-800mcg; 1-10 hours before termination) compared with the no cervical priming agent (± placebo)' group.

Comparison 2. Mifepristone versus misoprostol

Critical outcomes

Incomplete abortion

No evidence was identified to inform this outcome.

Cervical trauma

No evidence was identified to inform this outcome.

Uterine perforation

No evidence was identified to inform this outcome.

Important outcomes

Cumulative force required to sufficiently dilate cervix

RCT evidence showed there was no clinically important difference between the force required to dilate the cervix in the 'mifepristone' group (200mg; 24 hours before termination) and the 'misoprostol' group (800mcg; 2-4 hours before termination) (1 RCT, n=60; MD=-2.30N [95% CI -15.41, 10.81]; low quality).

Pre-operative pain

RCT evidence did not detect a clinically important difference in pre-operative pain between the 'mifepristone' group (200mg; 24 hours before termination) and the 'misoprostol' group (800mcg; 2-4 hours before termination) (1 RCT, n=89; RR=0.89 [95% CI 0.65, 1.23]; very low quality); however, there was uncertainty around the estimate.

Pre-operative expulsion

No evidence was identified to inform this outcome.

Pre-operative bleeding

RCT evidence did not detect a clinically important difference in pre-operative bleeding between the 'mifepristone' group (200mg; 24 hours before termination) and the 'misoprostol' group (800mcg; 2-4 hours before termination) (1 RCT, n=89; RR=1.29 [95% CI 0.37, 4.50]; very low quality); however, there was uncertainty around the estimate.

Comparison 3. Sublingual misoprostol 400mcg versus sublingual misoprostol 200mcg (both given 2-3 hours before termination)

Critical outcomes

Incomplete abortion

RCT evidence reported no events of incomplete abortion in either the 'sublingual misoprostol 400mcg' group or the 'sublingual misoprostol 200mcg' group (1 RCT, n=90; moderate quality); therefore, differences between groups could not be estimated.

Cervical trauma

No evidence was identified to inform this outcome.

Uterine perforation

RCT evidence reported no events of uterine perforation in either the 'sublingual misoprostol 400mcg' group or the 'sublingual misoprostol 200mcg' group (1 RCT, n=90; moderate quality); therefore, differences between groups could not be estimated.

Important outcomes

Ease of cervical dilation/force required to dilate cervix

No evidence was identified to inform this outcome.

Pre-operative pain

RCT evidence did not detect a clinically important difference in pre-operative pain between the 'sublingual misoprostol 400mcg' group and the 'sublingual misoprostol 200mcg' group (1 RCT, n=90; RR=1.21 [95% CI 0.80, 1.84]; low quality); however, there was uncertainty around the estimate.

Pre-operative expulsion

RCT evidence reported no events of pre-operative expulsion in either the 'sublingual misoprostol 400mcg' group or the 'sublingual misoprostol 200mcg' group (1 RCT, n=90; no events observed; moderate quality); therefore, differences between groups could not be estimated.

Pre-operative bleeding

RCT evidence did not detect a clinically important difference in pre-operative bleeding between the 'sublingual misoprostol 400mcg' group and the 'sublingual misoprostol 200mcg' group (1 RCT, n=90; RR=1.11 [95% CI 0.80, 1.54]; low quality); however, there was uncertainty around the estimate.

Comparison 4. Cervical priming agent A interval A versus cervical priming agent A interval B

Critical outcomes

Incomplete abortion

Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval

RCT evidence reported no events of incomplete abortion in either the '2hr interval' group or the '3hr interval' group (1 RCT, n=60; moderate quality); therefore, differences between groups could not be estimated.

Cervical trauma

Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence reported no events of cervical trauma in either the '1hr interval' group or the '3hr interval' group (1 RCT, n=91, nulliparous women; moderate quality); therefore, differences between groups could not be estimated.

Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence reported no events of cervical trauma in either the '1hr interval' group or the '3hr interval' group (1 RCT, n=87, nulliparous women; no events observed; moderate quality); therefore, differences between groups could not be estimated.

Uterine perforation

Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence reported no events of uterine perforation in either the '1hr interval' group or the '3hr interval' group (1 RCT, n=91, nulliparous women; moderate quality); therefore, differences between groups could not be estimated.

Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence reported no events of uterine perforation in either the '1hr interval' group or the '3hr interval' group (1 RCT, n=87, nulliparous women; moderate quality); therefore, differences between groups could not be estimated.

Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval

RCT evidence reported no events of uterine perforation in either the '2hr interval' group or the '3hr interval' group (1 RCT, n=60; moderate quality); therefore, differences between groups could not be estimated.

Important outcomes

Cumulative force required to sufficiently dilate cervix

Mifepristone (200mg): 24hr interval versus 48hr interval

RCT evidence showed a higher clinically important difference in the cumulative force required to dilate the cervix in the '24hr interval' group compared with the '48hr interval' group (1 RCT, n=60; MD=14.3N [95% CI 2.13, 26.47]; low quality).

Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence showed there was no clinically important difference between the cumulative force required to dilate the cervix in the '1hr interval' group and the '3hr interval' group (1 RCT, n=91, nulliparous women; MD=-2.50N [95% CI -14.05, 9.05]; high quality).

Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence showed a higher clinically important difference in the cumulative force required to dilate the cervix in the '1hr interval' group compared with the '3hr interval' group (1 RCT, n=87, nulliparous women; MD=17.5N [95% CI 5.88, 29.12]; moderate quality).

Pre-operative pain

Mifepristone (200mg): 24hr interval versus 48hr interval

RCT evidence did not detect a clinically important difference in pre-operative pain between the '24hr interval' group and the '48hr interval' group (1 RCT, n=60; RR=0.76 [95% CI 0.51, 1.15]; very low quality); however, there was uncertainty around the estimate.

Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence did not detect a clinically important difference in pre-operative pain between the '1hr interval' group and the '3hr interval' group (1 RCT, n=91, nulliparous women; RR=0.99 [95% CI 0.74, 1.32]; very low quality); however, there was uncertainty around the estimate.

Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence showed a lower clinically important difference in pre-operative pain in the '1hr interval' group compared with the '3hr interval' group (1 RCT, n=87, nulliparous women; RR=0.26 [95% CI 0.12-0.56]; moderate quality).

Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval

RCT evidence did not detect a clinically important difference in pre-operative pain between the '2hr interval' group and the '3hr interval' group (1 RCT, n=60; RR=0.85 [0.57, 1.27]; very low quality); however, there was uncertainty around the estimate.

Pre-operative expulsion

Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence reported no events of pre-operative expulsion in either the '1hr interval' group or the '3hr interval' group (1 RCT, n=91, nulliparous women; moderate quality); therefore, differences between groups could not be estimated.

Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence reported no events of pre-operative expulsion in either the '1hr interval' group or the '3hr interval' group (1 RCT, n=87, nulliparous women; moderate quality); therefore, differences between groups could not be estimated.

Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval

RCT evidence reported no events of pre-operative expulsion in either the '2hr interval' group or the '3hr interval' group (1 RCT, n=60; moderate quality); therefore, differences between groups could not be estimated.

Pre-operative bleeding

Mifepristone (200mg): 24hr interval versus 48hr interval

RCT evidence did not detect a clinically important difference in pre-operative bleeding between the '24hr interval' group and the '48hr interval' group (1 RCT, n=60; RR=0.33 [95% CI 0.07, 1.52]; very low quality); however, there was uncertainty around the estimate.

Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence showed a lower clinically important difference in pre-operative bleeding in the '1hr interval' group compared with the '3hr interval' group (1 RCT, n=91, nulliparous women; RR=0.14 [95% CI 0.03, 0.56]; moderate quality).

Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval

RCT evidence did not detect a clinically important difference in pre-operative bleeding between the '1hr interval' group and the '3hr interval' group (1 RCT, n=87, nulliparous; RR=0.38 [95% CI 0.11, 1.35]; low quality); however, there was uncertainty around the estimate.

Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval

RCT evidence did not detect a clinically important difference in pre-operative bleeding between the '2hr interval' group and the '3hr interval' group (1 RCT, n=60; RR=0.87 [95% CI 0.63, 1.20]; low quality); however, there was uncertainty around the estimate.

Comparison 5. Sublingual misoprostol versus vaginal misoprostol (both 400mcg; 1-3 hours before termination).

Critical outcomes

Incomplete abortion

RCT evidence reported no events of incomplete abortion in either the 'sublingual misoprostol' group or the 'vaginal misoprostol' group (1 RCT, n=100; low quality); therefore, differences between groups could not be estimated.

Cervical trauma

RCT evidence reported no events of cervical trauma in either the 'sublingual misoprostol' group or the 'vaginal misoprostol' group in women of mixed parity (1 RCT, n=1,258; moderate quality) or nulliparous women (1 RCT, n=178; moderate quality); therefore, differences between groups could not be estimated.

Uterine perforation

RCT evidence reported no events of uterine perforation in either the 'sublingual misoprostol' group or the 'vaginal misoprostol' group in women of mixed parity (2 RCTs, n=1,358; moderate quality) or nulliparous women (1 RCT, n=178; moderate quality); therefore, differences between groups could not be estimated.

Important outcomes

Cumulative force required to sufficiently dilate cervix

RCT evidence showed there was no clinically important difference between the cumulative force required to dilate the cervix in the 'sublingual misoprostol' group and the 'vaginal misoprostol' group (2 RCTs, n=257, nulliparous women; MD=1.76N [95% CI -1.43, 4.95]; moderate quality).

Ease of cervical dilation

RCT evidence did not detect a clinically important difference in the rate of women requiring no further dilation (RR=1.23 [95% CI 1.05, 1.44]; low quality), and the rates of further dilation being reported as 'easy' (RR=0.89 [95% CI 0.80, 0.99]; moderate quality), 'normal' (RR=1.05 [95% CI 0.79, 1.38]; very low quality), or 'difficult' (RR=0.66 [95% CI 0.36, 1.20]; low quality) by the operating physician between the 'sublingual misoprostol' group and the 'vaginal misoprostol' group (1 RCT, n=1,258); however, there was uncertainty around the estimates.

Pre-operative pain

RCT evidence did not detect a clinically important difference in any pre-operative pain (3 RCTs, n=300, women of mixed parity; RR=1.17 [95% CI 0.95, 1.43]; very low quality), mild pre-operative pain (1 RCT, n=80, nulliparous women; RR=1.29 [95% CI 0.82, 2.04]; very low quality), moderate pre-operative pain (1 RCT, n=80, nulliparous women; RR=1.22 [95% CI 0.57, 2.62]; very low quality), or severe pre-operative pain (1 RCT, n=80, nulliparous women; RR=0.20 [95% CI 0.02, 1.64]; very low quality) between the 'sublingual misoprostol' group and the 'vaginal misoprostol' group; however, there was uncertainty around the estimates. RCT evidence showed either a higher clinically important difference or did not detect a clinically important difference in any pre-operative pain between, the 'sublingual misoprostol' group and the 'vaginal misoprostol' group for nulliparous women (2 RCTs, n=258; very low quality). The evidence was not pooled due to high heterogeneity (Saav 2015 RR=1.94 [95% CI 1.41, 2.69]; Tang 2004 RR=1.10 [95% CI 0.89, 1.36]) and there was uncertainty around one of the estimates.

Pre-operative expulsion

RCT evidence reported no events of pre-operative expulsion in either the 'sublingual misoprostol' group or the 'vaginal misoprostol' group in women of mixed parity (2 RCTs, n=200; low quality) or nulliparous women (2 RCTs, n=258; low quality); therefore, differences between groups could not be estimated.

Pre-operative bleeding

RCT evidence showed a higher clinically important difference in any pre-operative bleeding in the 'sublingual misoprostol' group compared with the 'vaginal misoprostol' group in women of mixed parity (3 RCTs, n=300; RR=1.78 [95% CI 1.35, 2.36]; low quality). However, RCT evidence did not detect a clinically important difference in any pre-operative bleeding (2 RCTs, n=258; RR=1.56 [95% CI 0.95, 2.56]; low quality), minimal pre-operative bleeding (1 RCT, n=80; RR=1.71 [95% CI 0.75, 3.90]; very low quality), moderate pre-operative bleeding (1 RCT, n=80; RR=3.00 [95% CI 0.33, 27.63]; very low quality), or heavy pre-operative bleeding (1 RCT, n=80; RR=0.33 [95% CI 0.01, 7.95]; very low quality) between the 'sublingual misoprostol' group and the 'vaginal misoprostol' group in nulliparous women; however, there was uncertainty around the estimates.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of cervical priming is to soften and dilate the cervix to facilitate termination of pregnancy. If dilation is insufficient, there is an increased risk that the physician will not be able to adequately complete the abortion; therefore, incomplete abortion was selected as a critical outcome due to the impact of needing a second appointment will have on both the woman and on available resources. The committee agreed that although cervical trauma and uterine perforation are rare in women undergoing surgical termination of pregnancy, they should be prioritised as critical outcomes given the seriousness of such events.

The ease of, or force required for, cervical dilation was included as an important outcome as to assess the efficacy of cervical priming. Pre-operative pain, bleeding, and expulsion of the fetus were included to allow for a balance of the benefits and harms of priming as the likelihood of these occurring increases with the addition of cervical priming and with use of higher doses and are likely to impact patient satisfaction.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology. Evidence for incomplete abortion ranged from very low to high quality; the main reason evidence was downgraded was for imprecision due to wide confidence intervals caused by few events of interest but there was also some inconsistency across studies comparing misoprostol with no cervical priming. Evidence for cervical trauma and uterine perforation ranged from very low to moderate quality; as with incomplete abortion, the main reason evidence was downgraded was due to wide confidence intervals caused by few events of interest but there was also risk of bias caused by inadequate information regarding allocation concealment for studies comparing misoprostol with no cervical priming. Ease of, or force required for, cervical dilation was most commonly reported as the cumulative force (N) required to dilate the cervix and ranged from low to high quality. When reported in this way, the only reason evidence was downgraded was for imprecision due to wide confidence intervals. However, studies comparing sublingual and vaginal misoprostol measured ease of dilation with physicians self-reporting and were therefore downgraded for risk of bias due to the lack of physician blinding and the subjective nature of this outcome. Evidence for pre-operative pain and bleeding ranged from very low to high quality; the most common reasons

for downgrading evidence was risk of bias due to lack of blinding and insufficient information about random sequence generation and allocation concealment, and imprecision due to wide confidence intervals. Evidence for pre-operative expulsion was of low to moderate quality, mainly due to low, or no, events of interest.

Benefits and harms

There was evidence of a decreased incomplete termination rate for women that had cervical priming with misoprostol compared with those who received no cervical priming. Subgroup analyses revealed that this may be driven by a greater decrease in incomplete termination among parous women. However, there is a clinical expectation that it would be harder to dilate the cervix in nulliparous women; therefore the committee did not think it was possible to conclude that there was a sub-group of women who would not benefit from cervical priming. There was also evidence of reduced force required to dilate the cervix when misoprostol was used compared with no priming, which may increase ease of procedure for physicians and minimise the risk of cervical trauma and uterine perforation. There was no evidence comparing mifepristone with no cervical priming and only 1 study that compared mifepristone with misoprostol and it was unclear whether or not there were clinically meaningful differences on any outcomes; therefore, the committee recommended that misoprostol was offered for cervical priming.

The committee were aware that regimens that are more effective at achieving cervical priming will cause increased pain and bleeding associated with dilation. Therefore, it was important to minimise the amount, and/or time, of pain and bleeding. For both sublingual and vaginal misoprostol the committee recommended that 400mcg was used as there was a greater amount of evidence for the effectiveness of this regimen. Studies that compared 200mcg and 400mcg sublingual misoprostol were unclear whether or not there were clinically meaningful differences in pre-operative pain, bleeding, or expulsion, but there was no evidence available comparing ease of dilation; therefore, we could conclude that the side-effect profile may not be worse with a higher dose, but could not conclude that a lower dose achieves sufficient cervical priming. No recommendation was made about the use of buccal misoprostol as it was not used in any of the included studies and oral misoprostol was excluded from the review protocol as it is known to have a slower absorption time and greater side effects. Comparison between different intervals between administration of sublingual misoprostol and termination showed significantly less pre-operative bleeding when administered 1 hour before the termination compared with 3 hours before the termination, with unclear evidence of any other clinically meaningful differences. Therefore, the committee agreed that administering sublingual misoprostol 1 hour before the procedure was sufficient for adequate cervical priming to occur. However, greater force was needed when vaginal misoprostol was administered 1 hour before termination compared with 3 hours before; therefore, the committee recommended that a 3 hour interval is needed if vaginal misoprostol was used.

The committee agreed that mifepristone should be considered if there is a contraindication to misoprostol based on the limited evidence of unclear differences between cervical priming with mifepristone and with misoprostol. All of the studies included in the evidence review used 200mg oral mifepristone, which is standard clinical practice and the majority of studies administered mifepristone 24 hours before the termination. However, there was some evidence of less force needed to dilate the cervix when mifepristone is given 48 hours ahead of the termination compared with 24 hours before. Therefore, the committee recommended that 200mg oral mifepristone is given 24 to 48 hours before the termination.

Finally, the committee agreed that many women choose surgical termination over medical termination due to decreased pain and bleeding. However, women may choose the safer option of cervical priming at the cost of pain or bleeding as long as the risks and benefits are fully explained. Therefore, the committee recommended that women are made aware of the

risk and benefits of cervical priming, particularly of the associated pre-operative bleeding and pain.

As there was sufficient evidence to inform the recommendations, the committee decided to prioritise other areas addressed by the guideline for future research and therefore made no research recommendations regarding cervical priming before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed the potential costs and savings of recommendations and thought that there would be an increased cost associated with recommendations as cervical priming is not currently consistently used before 14^{+0} weeks' gestation. However, it is unclear how large such an increase in cost would be as cervical priming is used as standard practice in Scotland and it is not known how many services in England are currently offering cervical priming for surgical termination during the first trimester. The committee agreed that the increased cost may in part be offset by savings due to fewer additional operations needed for incomplete abortion. Overall the committee did not consider there were likely to be significant resource implications from making these recommendations.

Other consideration

The committee agreed that current inequalities, in terms of reduced access experienced by women living in remote areas may be reduced by recommending the option of sublingual misoprostol administered 1 hour before termination as it will minimise how long before the termination women are required to arrive at hospital and may reduce the needed for overnight stays and maximise the number of women receiving optimal cervical priming.

The committee also thought it was important to make women aware of analgesia that could ameliorate any pre-operative pain experienced. However, they were unable to make recommendations in this area as the use of analgesia was not considered as part of this review question.

Cervical priming before surgical termination of pregnancy

Cervical priming between 14^{+0} and 24^{+0} weeks' gestation

Review question

What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

Introduction

The aim of this review is to determine the optimal cervical priming regimen (if any) before surgical termination of pregnancy between 14^{+0} and $24+^{0}$ weeks' gestation

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 4: Summary of the protocol (PICO table)

Population	Women who are having surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation.
Intervention	Cervical priming agents: • Mifepristone (oral) • Misoprostol (oral, vaginal, sublingual, buccal) • Osmotic cervical dilators
Comparison	• Cervical priming agent A versus cervical priming agent B • Cervical priming agents (combination of any 2 or 3) versus cervical priming agent (single) • Cervical priming agents (combination of any 2 or 3) versus cervical priming agents (combination of any 2 or 3) • Cervical priming agent A – dose A versus cervical priming agent A – dose B • Cervical priming agent A – interval A versus cervical priming agent A – interval B • Misoprostol route A versus misoprostol route B
Outcome	**Critical outcomes:** • Baseline cervical dilation • Cervical trauma • Uterine perforation **Important outcomes:** • Pre-operative expulsion • Ease of procedure (measured using Likert scale) • Patient acceptability • Duration of procedure

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

Only studies conducted from 1985 onwards were considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991.

Thirteen randomised controlled trials (RCTs; number of participants, n=2,242) were included in the review (Boraas 2016; Borgatta 2012; Carbonell 2007; Casey 2016; Drey 2014; Edelman 2006; Goldberg 2005; Goldberg 2015; Grossman 2014; Newmann 2014; Sagiv 2015; Shaw 2015; Shaw 2017).

Four RCTs compared a single priming agent against another single priming agent (osmotic dilators ± placebo versus misoprostol [n=3; Goldberg 2005; Grossman 2014; Sagiv 2015], osmotic dilators versus mifepristone [n=1; Borgatta 2012]). Six RCTs compared a combination of cervical priming agents against a single priming agent (osmotic dilators + buccal misoprostol versus osmotic dilators ± placebo [n=4; Boraas 2016; Drey 2014; Edelman 2006; Goldberg 2015], osmotic dilators + mifepristone versus osmotic dilators [n=1; Goldberg 2015], sublingual misoprostol + mifepristone versus sublingual misoprostol [n=1; Carbonell 2007], vaginal misoprostol + mifepristone versus vaginal misoprostol [n=2; Carbonell 2007; Casey 2016]). Three RCTs compared a combination of cervical priming agents against a different combination of cervical priming agents (osmotic dilators + buccal misoprostol + mifepristone versus osmotic dilators + buccal misoprostol ± placebo [n=2; Shaw 2015; Shaw 2017], osmotic dilators + buccal misoprostol + mifepristone versus buccal misoprostol + mifepristone [n=1; Shaw 2017], osmotic dilators + buccal misoprostol + placebo versus buccal misoprostol + mifepristone [n=1; Shaw 2017], osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone [n=1; Goldberg 2015]). One RCT compared overnight osmotic dilators against same-day osmotic dilators (Newmann 2014). One RCT compared sublingual misoprostol against vaginal misoprostol (sublingual misoprostol + mifepristone versus vaginal misoprostol + mifepristone [n=1; Carbonell 2007], sublingual misoprostol versus vaginal misoprostol [n=1; Carbonell 2007]).

Three RCTs (Edelman 2006; Grossman 2014; Newmann 2014) reported data for subgroups of interest: nulliparous [n=3], parous [n=3]. Twelve of the 13 RCTs only included women aged 18 years and older; 1 trial included women from age 15 but data was not presented separately for those aged under 18. There was no subgroup data available based on medical conditions or previous caesarean sections.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 5: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Boraas 2016	n=29	**Osmotic dilators + buccal**	• Baseline cervical dilation	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
RCT USA	English speaking women age 18 years or above, undergoing dilatation and evacuation (D&E) 16^{+0} to 20^{+6} weeks' gestation	**misoprostol:** dilators administered minimum of 4 hours before D&E; 400micrograms (mcg) buccal misoprostol 3 hours before D&E **Osmotic dilators + placebo:** dilators administered minimum of 4 hours before D&E; buccal administration of 4 folic acid tablets 3 hours before D&E	• Cervical lacerations • Patient acceptability • Duration of procedure	
Borgatta 2012 RCT USA	n=50 Women aged 18 to 45 years requesting termination 14 to 16 weeks' gestation	**Osmotic dilators**: 3 to 6 dilators administered following oral pain relief and paracervical block 20 to 24 hours before termination **Mifepristone:** 200mg oral mifepristone given 20 to 24 hours before termination	• Baseline cervical dilation (14mm cannula passed without additional dilation) • Pre-operative expulsion • Ease of procedure • Patient acceptability • Duration of procedure	
Carbonell 2007 RCT Spain	n=900 Women requesting termination and willing to abstain from sexual intercourse for 14 days after 12 to 20 weeks' gestation	**Sublingual misoprostol + mifepristone:** 200mg oral mifepristone given 48 hours before 600mcg sublingual misoprostol, which was given 1.5 to 2.5 hours before termination **Vaginal misoprostol + mifepristone:** 200mg oral	• Baseline cervical dilation • Pre-operative expulsion • Duration of procedure	Serious indirectness; includes women with gestational age from 2 weeks lower than population of interest for this question

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		mifepristone given 48 hours before 600mcg vaginal misoprostol, which was given 1.5 to 2.5 hours before termination **Sublingual misoprostol:** 600mcg sublingual misoprostol given 1.5 to 2.5 hours before termination **Vaginal misoprostol:** 600mcg vaginal misoprostol given 1.5 to 2.5 hours before termination		
Casey 2016 RCT USA	n=100 Women aged 18 years or above requesting D&E 14 to 19^{+6} weeks' gestation	**Misoprostol + mifepristone:** 200mg oral mifepristone and 400mcg vaginal misoprostol given 4 to 6 hours before D&E **Misoprostol + placebo:** placebo and 400mcg vaginal misoprostol given 4 to 6 hours before D&E	• Baseline cervical dilation • Cervical injury • Uterine perforation • Pre-operative expulsion • Ease of procedure • Patient acceptability • Duration of procedure	
Drey 2014 RCT USA	n=196 English and Spanish speaking women aged 18 years or above requesting D&E 21^{+0} to 23^{+1} weeks' gestation	**Osmotic dilators + misoprostol:** laminaria were inserted the day before scheduled D&E and 400mcg buccal misoprostol was given 3 to 4 hours before D&E **Osmotic dilators + placebo:** laminaria were inserted the day	• Cervical lacerations requiring suturing • Uterine perforation • Pre-operative expulsion • Ease of procedure • Duration of procedure	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		before scheduled D&E and 100mcg B6 (placebo) was given 3 to 4 hours before D&E		
Edelman 2006 RCT USA	n=138 English speaking women aged 18 years or above requesting termination 13^{+0} to 20^{+6} weeks' gestation	**Osmotic dilators + misoprostol:** laminaria were placed the day before scheduled termination and 400mcg misoprostol was taken bucally 60 to 90 minutes before termination **Osmotic dilators + placebo:** laminaria were placed the day before scheduled termination and 500mg magnesium oxide (placebo) was taken bucally 60 to 90 minutes before termination	• Baseline cervical dilation • Duration of procedure	Serious indirectness; includes women with gestational age from 1 week lower than population of interest for this question
Goldberg 2005 RCT USA	n=84 English or Spanish speaking women aged 18 years or above who decided to have an outpatient termination 12^{+6} to 15^{+6} weeks' gestation	**Osmotic dilators + placebo**: 3 to 6 laminaria were placed the day before the termination and 3 to 4 hours before the termination 2 B6 tablets (placebo) were placed in the vagina **Misoprostol:** 400mcg misoprostol was placed in the vagina 3 to 4 hours before the termination	• Baseline cervical dilation • Ease of procedure • Patient acceptability	Serious indirectness; includes women with gestational age from 1 week lower than population of interest for this question
Goldberg 2015 RCT USA	n=300 16^{+0} to 23^{+6} weeks' gestation	**Osmotic dilators + misoprostol:** oral placebo was given the day before the termination and	• Baseline cervical dilation • Cervical lacerations requiring suturing	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		osmotic dilators were inserted. The following day, approximately 3 hours before the termination, 400mcg buccal misoprostol was given **Osmotic dilators + mifepristone:** 200mg oral mifepristone was given the day before the termination and osmotic dilators were inserted. The following day, approximately 3 hours before the termination, buccal placebo was given **Osmotic dilators:** oral placebo was given the day before the termination and osmotic dilators were inserted. The following day, approximately 3 hours before the termination, buccal placebo was given	• Uterine perforation • Pre-operative expulsion • Ease of procedure • Patient acceptability • Duration of procedure	
Grossman 2014 RCT South Africa	n=159 English, Afrikaans or Xhosa speaking women aged 18 years or above requesting D&E 13^{+0} to 19^{+0} weeks' gestation	**Osmotic dilators:** the day before termination 3 to 7 laminaria were inserted following a paracervical block **Misoprostol:** women were given 400mcg misoprostol the day before the termination and	• Uterine perforation (suspected) • Pre-operative expulsion • Duration of procedure	Serious indirectness; includes women with gestational age from 1 week lower than population of interest for this question

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		instructed to administer them bucally at 5am the following morning		
Newmann 2014 RCT USA	n=72 English and Spanish speaking women aged 18 years or above 13^{+6} to 17^{+6} weeks' gestation	**Overnight osmotic dilators:** laminaria were placed the day prior to termination following a paracervical block **Same-day osmotic dilators:** laminaria were placed on the same day as termination (4 to 6 hours before) following a paracervical block	• Baseline cervical dilation • Cervical trauma • Ease of procedure (inadequate dilation) • Patient acceptability • Duration of procedure	
Sagiv 2015 RCT Israel	n=84 Women aged 15 years or above, in good general health, requesting termination 13 to 20 weeks' gestation	**Osmotic dilators:** 1 to 6 laminaria were placed at midnight before the termination; no paracervical anaesthesia was used **Misoprostol:** 600mcg misoprostol was administered vaginally at midnight before the termination	• Baseline cervical dilation • Pre-operative expulsion	Serious indirectness; includes women with gestational age from 1 week lower than population of interest for this question
Shaw 2015` RCT USA	n=50 English or Spanish speaking women aged 18 years or above presenting for outpatient termination 19^{+0} to 23^{+6} weeks' gestation	**Osmotic dilators + misoprostol + mifepristone:** The day before termination 200mg mifepristone was given and had 4 to 5 dilators placed after administration of a paracervical block; 400mcg	• Duration of procedure	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		buccal misoprostol was given 90 minutes before the termination **Osmotic dilators + misoprostol:** 2 to 4 dilators were placed, after administration of a paracervical block, 2 days before the termination; the following day, an additional 4 to 5 dilators were placed. 400mcg buccal misoprostol was given 90 minutes before the termination		
Shaw 2017 RCT USA	n=80 English or Spanish speaking women aged 18 years or above with a viable singleton pregnancy requesting surgical termination 19^{+0} to 23^{+6} weeks' gestation	**Osmotic dilators + mifepristone + misoprostol:** 3 to 5 dilators were placed the day before termination, following a paracervical block, and 200mg oral mifepristone was given; 400mcg buccal misoprostol was given 90 minutes before the termination **Osmotic dilators + misoprostol + placebo:** 3 to 5 dilators were placed the day before termination, following a paracervical block, and an oral placebo was given; 400mcg buccal misoprostol was given 90 minutes	• Baseline cervical dilation • Cervical lacerations • Uterine perforation	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		before the termination **Misoprostol + mifepristone:** 200mg oral mifepristone was given the day before the termination and 400mcg buccal misoprostol was given 2 to 3 hours before the termination		

D&E: dilatation and evacuation; mcg: micrograms; RCT: randomised controlled trial

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Resource impact

Table 6: Unit Costs

Resource	Unit costs	Source
Hourly Cost Nurse including on costs	£21.56	BPAS Correspondence
Staff cost per additional priming (assume 45 minutes)	£16.17	BPAS Correspondence

Resource	Unit costs	Source
Misoprostol 7 microgram per 1 hour	£93.00 per unit	BNF 75
Mifepristone 200mg	£17.55 per unit	BNF 75

BNF: British National Formulary; BPAS: British Pregnancy Advisory Service

All unit costs and cost estimates for staff time presented above are based on correspondence with the British Pregnancy Advisory Service (BPAS). BPAS is not a NHS organisation although the majority of terminations carried out at their clinics are NHS funded. The costs therefore may not accurately reflect those to the NHS although should give an estimate of size and magnitude of the above activites. The committee would expect given the economies of scale and specialisation that BPAS are able to exploit in this area that the costs above are likely to be an underestimate of the costs of providing these activities in an NHS setting.

The committee highlighted that if cervical priming was to be offered here would be an increase in contact time with staff. Therefore there would need to be either an increase in staffing or a reduction in the capacity and number of terminations that could be given. The unit costs above focus on increased staffing given the equity considerations for any NICE recommendation.

Drug costs are taken from the BNF. Again the committee highlighted that the price paid by BPAS or other similar organisations is likely to be significantly lower especially for misoprostol where an estimated cost of less than £2 per termination was estimated by BPAS.

Evidence statements

Comparison 1. Single agent A versus single agent B

Critical outcomes

Baseline cervical dilation

Osmotic dilators (± placebo) versus misoprostol

RCT evidence either did not detect a clinically important difference or showed there was no clinically important difference in baseline cervical dilation between the ‘osmotic dilators (± placebo)’ group and the ‘misoprostol’ group (400-600mcg; at least 3 hours before termination) (2 RCTs, n=167; very low quality). The evidence was not pooled due to high heterogeneity (Goldberg 2005 MD=3.30mm [95% CI 2.22, 4.38]; Sagiv 2015 MD=0.40mm [95% CI -0.59, 1.39]) and there was uncertainty around one of the estimates.

Osmotic dilators versus mifepristone

RCT evidence showed a higher clinically important difference in the rate of passing a 14mm cannula without additional dilation in the ‘osmotic dilators’ group compared with the ‘mifepristone’ group (200mg; 20-24 hours before termination) (1 RCT, n=49; RR=18.75 [95% CI 2.71, 129.72]; high quality).

Cervical trauma

Osmotic dilators (± placebo) versus misoprostol

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the ‘osmotic dilators (± placebo)’ group and the ‘misoprostol’ group (400mcg; 3-4

hours before termination) (1 RCT, n=83; RR=0.20 [95% CI 0.01, 3.95] very low quality); however, there was uncertainty around the estimate.

Uterine perforation

Osmotic dilators (± placebo) versus misoprostol

RCT evidence did not detect a clinically important difference in the rate of uterine perforation between the 'osmotic dilators (± placebo)' group and the 'misoprostol' group (400mcg; at least 3 hours before termination) (2 RCTs, n=239; RR=0.33 [95% CI 0.03, 3.12]; very low quality); however, there was uncertainty around the estimate.

Important outcomes

Pre-operative expulsion

Osmotic dilators (± placebo) versus misoprostol

RCT evidence did not detect a clinically important difference in the rate of pre-operative expulsion between the 'osmotic dilators (± placebo)' group and the 'misoprostol' group (400-600mcg) (2 RCTs, n=240; RR=0.24 [95% CI 0.03, 2.17]; very low quality); however, there was uncertainty around the estimate.

Osmotic dilators versus mifepristone

RCT evidence did not detect a clinically important difference in the rate of pre-operative expulsion between the 'osmotic dilators' group and the 'mifepristone' group (200mg; 20-24 hours before termination) (1 RCT, n=50; RR=3.0 [95% CI 0.13, 70.3]; low quality); however, there was uncertainty around the estimate.

Ease of procedure – rated as not difficult

Osmotic dilators (± placebo) versus misoprostol

RCT evidence showed a higher clinically important difference in the rate of physicians rating the procedure as 'not difficult' in the 'osmotic dilators (± placebo)' group compared with the 'misoprostol' group (400mcg; 3-4 hours before termination) (1 RCT, n=83; RR=1.89 [95% CI 1.2, 2.96]; low quality).

Osmotic dilators versus mifepristone

RCT evidence did not detect a clinically important difference in the rate of physicians rating the procedure as 'not difficult' between the 'osmotic dilators' group and the 'mifepristone group (200mg; 20-24 hours before termination) (1 RCT, n=49; RR=1.27 [95% CI 0.65, 2.51]; very low quality); however, there was uncertainty around the estimate.

Ease of procedure – rated as mildly difficult

Osmotic dilators (± placebo) versus misoprostol

RCT evidence did not detect a clinically important difference in the rate of physicians rating the procedure as 'mildly difficult' between the 'osmotic dilators (± placebo)' group and the 'misoprostol' group (400mcg; 3-4 hours before termination) (1 RCT, n=83; RR=0.65 [95% CI 0.33, 21.28]; very low quality); however, there was uncertainty around the estimate.

Ease of procedure – rated as difficult

Osmotic dilators versus mifepristone

RCT evidence did not detect a clinically important difference in the rate of physicians rating the procedure as 'difficult' between the 'osmotic dilators' group and the 'mifepristone' group (200mg; 20-24 hours before termination) (1 RCT, n=49; RR=0.35 [95% CI 0.08, 1.55]; very low quality); however, there was uncertainty around the estimate.

Ease of procedure – rated as moderately/markedly difficult

Osmotic dilators (± placebo) versus misoprostol

RCT evidence showed a lower clinically important difference in the rate of physicians rating the procedure as 'moderately/markedly difficult' in the 'osmotic dilators (± placebo)' group compared with the 'misoprostol' group (400mcg; 3-4 hours before termination) (1 RCT, n=83; RR=0.18 [95% CI 0.04, 0.75]; moderate quality).

Patient acceptability – would choose same method again

Osmotic dilators (± placebo) versus misoprostol

RCT evidence showed a lower clinically important difference in the rate of women who would choose the same method again in the 'osmotic dilators (± placebo)' group compared with the 'misoprostol' group (400mcg; 3-4 hours before termination) (1 RCT, n=83; RR=0.67 [95% CI 0.52, 0.86]; low quality).

Osmotic dilators versus mifepristone

RCT evidence showed a lower clinically important difference in the rate of women who would choose the same method again in the 'osmotic dilators' group compared with the 'mifepristone' group (200mg; 20-24 hours before termination) (1 RCT, n=49; RR=0.3 [95% CI 0.16, 0.57]; moderate quality).

Patient acceptability – would prefer 1-day misoprostol to 2-day dilators

Osmotic dilators (± placebo) versus misoprostol

RCT evidence did not detect a clinically important difference in the rate of women who would prefer 1-day misoprostol to 2-day dilators between the 'osmotic dilators (± placebo)' group and the 'misoprostol' group (400mcg; 3-4 hours before termination) (1 RCT, n=83; RR=0.87 [95% CI 0.71, 1.06]; low quality); however, there was uncertainty around the estimate.

Duration of procedure (minutes) – speculum in to speculum out

Osmotic dilators versus mifepristone

RCT evidence did not detect a clinically important difference in duration of procedure between the 'osmotic dilators' group and the 'mifepristone' group (200mg; 20-24 hours before termination) (1 RCT, n=49; MD=-1.87 minutes [95% CI -4.39, 0.65]; moderate quality); however, there was uncertainty around the estimate.

Osmotic dilators (± placebo) versus misoprostol

RCT evidence did not detect a clinically important difference in duration of procedure between the 'osmotic dilators (± placebo)' group and the 'misoprostol' group (400mcg) in nulliparous women (1 RCT, n=40; MD=-0.20 minutes [95% CI -3.27, 2.87]; low quality); however, there was uncertainty around the estimate. RCT evidence showed there was no

clinically important difference between duration of procedure in the 'osmotic dilators (± placebo)' group and the 'misoprostol' group in parous women (1 RCT, n=116; MD=0.50 minutes [95% CI -1.76, 2.76]; moderate quality).

Duration of procedure (minutes) – beginning of suction to speculum out

Osmotic dilators versus mifepristone

RCT evidence showed there was no clinically important difference between duration of procedure in the 'osmotic dilators' group and the 'mifepristone' group (200mg; 20-24 hours before termination) (1 RCT, n=49; MD=-0.2 minutes [95% CI -1.72, 1.32]; high quality).

Comparison 2. Combination of agents versus single agent

Critical outcomes

Baseline cervical dilation

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence showed there was no clinically important difference between baseline cervical dilation in the 'osmotic dilators + buccal misoprostol' group (400mcg; 1-3 hours before termination) and the 'osmotic dilators (± placebo)' group in women of mixed parity (2 RCTs, n=351; MD=0.98mm [-0.14, 2.11]; moderate quality), nulliparous women (1 RCT, n=40; MD=0.90mm [-0.28, 2.08]; moderate quality), or parous women (1 RCT, n=86; MD=0.2mm [-0.56, 0.96]; moderate quality).

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence showed there was no clinically important difference between baseline cervical dilation in the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) and the 'osmotic dilators' group (1 RCT, n=197; MD=0.20cm [95% CI 0.06, 0.34]; high quality).

Sublingual misoprostol + mifepristone versus sublingual misoprostol

RCT evidence did not detect a clinically important difference in baseline cervical dilation between the 'sublingual misoprostol + mifepristone' group (misoprostol 600mcg; 1.5-2.5 hours before termination; mifepristone 200mg; 48 hours before termination) and the 'sublingual misoprostol' group (1 RCT, n=438; MD=3.70mm [95% CI 3.21, 4.19]; low quality); however, there was uncertainty around the estimate.

Vaginal misoprostol + mifepristone versus vaginal misoprostol

RCT evidence showed either a higher clinically important difference or showed there was no clinically important difference in baseline cervical dilation between the 'vaginal misoprostol + mifepristone' group (misoprostol 400-600mcg; 1.5-6 hours before termination; mifepristone 200mg; 4-48 hours before termination) (2 RCTs, n=535; very low quality).The evidence was not pooled due to high heterogeneity (Carbonell 2007 MD=4.30 [95% CI 3.68, 4.92]; Casey 2016 MD=0.80 [95% CI -0.38, 1.98]).Cervical trauma

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3-4 hours before

termination) and the 'osmotic dilators (± placebo)' group (3 RCTs, n=423; RR=0.71 [95% CI 0.13, 3.96]; very low quality); however, there was uncertainty around the estimate.

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) and the 'osmotic dilators' group (1 RCT, n=198; RR=0.14 [95% CI 0.01, 2.73] low quality); however, there was uncertainty around the estimate.

Vaginal misoprostol + mifepristone versus vaginal misoprostol (± placebo)

RCT evidence reported no events of cervical trauma in either the 'vaginal misoprostol + mifepristone' group (misoprostol 400mcg; 4-6 hours before termination; mifepristone 200mg; 4-6 hours before termination) or the 'vaginal misoprostol (± placebo)' group (1 RCT, n=96; moderate quality); therefore, differences between groups could not be estimated.

Uterine perforation

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence did not detect a clinically important difference in the rate of uterine perforation between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3-4 hours before termination) and the 'osmotic dilators (± placebo)' group (2 RCTs, n=393; RR=1.68 [95% CI 0.22, 12.59]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence reported no events of uterine perforation in either the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) or the 'osmotic dilators' group (1 RCT, n=197; moderate quality); therefore, differences between groups could not be estimated.

Vaginal misoprostol + mifepristone versus vaginal misoprostol (± placebo)

RCT evidence reported no events of uterine perforation in either the 'vaginal misoprostol + mifepristone) group (misoprostol 400mcg; 4-6 hours before termination; mifepristone 200mg; 4-6 hours before termination) or the 'vaginal misoprostol (± placebo) group (1 RCT, n=96; moderate quality); therefore, differences between groups could not be estimated.

Important outcomes

Pre-operative expulsion

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence did not detect a clinically important difference in the rate of pre-operative expulsion between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3-4 hours before termination) and the 'osmotic dilators (± placebo)' group (2 RCTs, n=394; RR=3.00 [95% CI 0.31, 28.60]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence reported no events of pre-operative expulsion in either the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) or the 'osmotic dilators' group (1 RCT, n=198; moderate quality); therefore, differences between groups could not be estimated.

Sublingual misoprostol + mifepristone versus sublingual misoprostol

RCT evidence showed a higher clinically important difference in the rate of pre-operative expulsion in the 'sublingual misoprostol + mifepristone' group (misoprostol 600mcg; 1.5-2.5 hours before termination; mifepristone 200mg; 48 hours before termination) compared with the 'sublingual misoprostol' group (1 RCT, n=450; RR=10.00 [95% CI 1.29, 77.47]; moderate quality).

Vaginal misoprostol + mifepristone versus vaginal misoprostol (± placebo)

RCT evidence did not detect a clinically important difference in the rate of pre-operative expulsion between the 'vaginal misoprostol + mifepristone' group (misoprostol 400-600mcg; 1.5-6 hours before termination; mifepristone 200mg; 4-48 hours before termination) and the 'vaginal misoprostol (± placebo)' group (2 RCTs, n=547; RR=3.39 [95% CI 0.84, 13.74]; low quality); however, there was uncertainty around the estimate.

Ease of procedure – agree/strongly agree easy to perform

Vaginal misoprostol + mifepristone versus vaginal misoprostol (± placebo)

RCT evidence showed there was no clinically important difference between the rate of physicians agreeing the procedure was easy to perform in the 'vaginal misoprostol + mifepristone' group (misoprostol 400mcg; 4-6 hours before termination; mifepristone 200mg; 4-6 hours before termination) and the 'vaginal misoprostol (± placebo)' group (1 RCT, n=95; RR=1.03 [95% CI 0.88, 1.21]; high quality).

Ease of procedure – rated as (very/extremely) difficult to perform

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence did not detect a clinically important difference in the rate of physicians rating the procedure '(very/extremely) difficult to perform' between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3-4 hours before termination) and the 'osmotic dilators (± placebo)' group (2 RCTs, n=393; RR=0.77 [95% CI 0.46, 1.28]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence showed a lower clinically important difference in the rate of physicians rating the procedure '(very/extremely) difficult to perform' in the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) compared with the 'osmotic dilators' group (1 RCT, n=197; RR=0.20 [95% CI 0.06, 0.68]; high quality).

Patient acceptability – satisfied/very satisfied with priming

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence showed there was no clinically important difference between the rate of satisfaction with priming in the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators (± placebo)' group (2 RCTs, n=228; RR=1.05 [95% CI 0.91, 1.21]; high quality).

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence did not detect a clinically important difference in the rate of satisfaction with priming between the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) and the 'osmotic dilators' group (1 RCT, n=198; RR=1.11 [95% CI 0.95, 1.30]; moderate quality); however, there was uncertainty around the estimate.

Patient acceptability – dissatisfied/very dissatisfied with priming

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence did not detect a clinically important difference in the rate of dissatisfaction with priming between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators (± placebo)' group (2 RCTs, n=228; RR=0.72 [95% CI 0.23, 2.19]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence did not detect a clinically important difference in the rate of dissatisfaction between the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) and the 'osmotic dilators' group (1 RCT, n=198; RR=0.67 [95% CI 0.19, 2.29]; low quality); however, there was uncertainty around the estimate.

Patient acceptability – would choose same method again

Vaginal misoprostol + mifepristone versus vaginal misoprostol (± placebo)

RCT evidence showed there was no clinically important difference between the rate of women who would choose the method again in the 'vaginal misoprostol + mifepristone' group (misoprostol 400mcg; 4-6 hours before termination; mifepristone 200mg; 4-6 hours before termination) and the 'vaginal misoprostol (± placebo)' group (1 RCT, n=95; RR=1.00 [95% CI 0.90, 1.11]; high quality).

Patient acceptability – would recommend priming method to a friend

Vaginal misoprostol + mifepristone versus vaginal misoprostol (± placebo)

RCT evidence showed there was no clinically important difference between the rate of women who would recommend the priming method to a friend in the 'vaginal misoprostol + mifepristone' group (misoprostol 400mcg; 4-6 hours before termination; mifepristone 200mg; 4-6 hours before termination) and the 'vaginal misoprostol (± placebo)' group (1 RCT, n=95; RR=1.05 [95% CI 0.90, 1.23]; high quality).

Duration of procedure (minutes) – first instrument in to last instrument out

Osmotic dilators + buccal misoprostol versus osmotic dilators (± placebo)

RCT evidence showed there was no clinically important difference between duration of procedure in the 'osmotic dilators + buccal misoprostol' group (400mcg; 1-4 hours before termination) and the 'osmotic dilators (± placebo)' group (4 RCTs, n=546; MD=-0.74 minutes [95% CI -1.97, 0.48]; low quality).

Osmotic dilators + mifepristone versus osmotic dilators

RCT evidence showed there was no clinically important difference between duration of procedure in the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) and the 'osmotic dilators' group (1 RCT, n=197; (MD=-0.74 minutes [95% CI -1.64, 0.16]; high quality).

Duration of procedure (minutes) – anaesthesia administered to speculum out

Sublingual misoprostol + mifepristone versus sublingual misoprostol

RCT evidence showed there was no clinically important difference between duration of procedure in the 'sublingual misoprostol + mifepristone' group (misoprostol 600mcg; 1.5-2.5

hours before termination; mifepristone 200mg; 48 hours before termination) and the 'sublingual misoprostol' group (1 RCT, n=438; MD=-1.10 minutes [95% CI -2.00, -0.20]; moderate quality).

Vaginal misoprostol + mifepristone versus vaginal misoprostol (± placebo)

RCT evidence showed there was no clinically important difference between duration of procedure in the 'vaginal misoprostol + mifepristone' group (misoprostol 600mcg; 1.5-2.5 hours before termination; mifepristone 200mg; 48 hours before termination) and the 'vaginal misoprostol (± placebo)' group (2 RCTs, n=535; MD=-0.74 minutes [95% CI -1.75, 0.27]; moderate quality).

Comparison 3. Combination A versus combination B

Critical outcomes

Baseline cervical dilation

Osmotic dilators + buccal misoprostol + mifepristone versus osmotic dilators + buccal misoprostol (± placebo)

RCT evidence did not detect a clinically important difference in the rate of women with a baseline cervical dilation of at least 3cm between the 'osmotic dilators + buccal misoprostol + mifepristone' group (misoprostol 400mcg; 1.5-3 hours before termination; mifepristone 200mg; 24 hours before termination) and the 'osmotic dilators + buccal misoprostol (± placebo)' group (1 RCT, n=48; RR=0.91 [95% CI 0.54, 1.52]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol + mifepristone versus buccal misoprostol + mifepristone

RCT evidence showed a higher clinically important difference in the rate of women with a baseline cervical dilation of at least 3cm in the 'osmotic dilators + buccal misoprostol + mifepristone' group (misoprostol 400mcg; 1.5-3 hours before termination; mifepristone 200mg; 24 hours before termination) compared with the 'buccal misoprostol + mifepristone' group (1 RCT, n=54; RR=14.00 [95% CI 1.98, 99.13]; high quality).

Osmotic dilators + buccal misoprostol + placebo versus buccal misoprostol + mifepristone

RCT evidence showed a higher clinically important difference in the rate of women with a baseline cervical dilation of at least 3cm in the 'osmotic dilators + buccal misoprostol + placebo' group (misoprostol 400mcg; 1.5-3 hours before termination; mifepristone 200mg; 24 hours before termination) compared with the 'buccal misoprostol + mifepristone' group (1 RCT, n=48; RR=15.43 [95% CI 2.18, 109.39]; high quality).

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence showed there was no clinically important difference between baseline cervical dilation in the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=195; MD=0.1cm [95% CI -0.1, 0.3]; high quality).

Cervical trauma

Osmotic dilators + buccal misoprostol + mifepristone versus buccal misoprostol + mifepristone

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the 'osmotic dilators + buccal misoprostol + mifepristone' group (misoprostol 400mcg; 1.5-3 hours before termination; mifepristone 200mg; 24 hours before termination) and the 'buccal misoprostol + mifepristone' group (1 RCT, n=54; RR=0.09 [95% CI 0.01, 1.57]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol + mifepristone versus osmotic dilators + buccal misoprostol (± placebo)

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the 'osmotic dilators + buccal misoprostol + mifepristone' group (misoprostol 400mcg; 1.5-3 hours before termination; mifepristone 200mg; 24 hours before termination) and the 'osmotic dilators + buccal misoprostol (± placebo)' group (1 RCT, n=48; RR=0.26 [95% CI 0.01, 6.12]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol + placebo versus buccal misoprostol + mifepristone

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the 'osmotic dilators + buccal misoprostol + placebo' group (400mcg; 1.5-3 hours before termination) and the 'buccal misoprostol + mifepristone' group (mifepristone 200mg; 24 hours before termination) (1 RCT, n=48; RR=0.26 [95% CI 0.03, 2.04]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence reported no events of cervical trauma in either the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) or the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=199; moderate quality); therefore, differences between groups could not be estimated.

Uterine perforation

Osmotic dilators + buccal misoprostol + mifepristone versus osmotic dilators + buccal misoprostol (± placebo)

RCT evidence did not detect a clinically important difference in the rate of uterine perforation between the 'osmotic dilators + buccal misoprostol + mifepristone' group (misoprostol 400mcg; 1.5-3 hours before termination; mifepristone 200mg; 24 hours before termination) and the 'osmotic dilators + buccal misoprostol (± placebo)' group (1 RCT, n=48; RR=2.36 [95% CI 0.10, 55.09]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol + mifepristone versus buccal misoprostol + mifepristone

RCT evidence did not detect a clinically important difference in the rate of uterine perforation between the 'osmotic dilators + buccal misoprostol + mifepristone' group (misoprostol 400mcg; 1.5-3 hours before termination; mifepristone 200mg; 24 hours before termination) and the 'buccal misoprostol + mifepristone' group (1 RCT, n=54; RR=0.50 [95% CI 0.05, 5.19]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol + placebo versus buccal misoprostol + mifepristone

RCT evidence did not detect a clinically important difference in the rate of uterine perforation between the 'osmotic dilators + buccal misoprostol + placebo' group (400mcg; 1.5-3 hours before termination) and the 'buccal misoprostol + mifepristone' group (mifepristone 200mg; 24 hours before termination) (1 RCT, n=48; RR=0.25 [95% CI 0.01, 5.03]; low quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence did not detect a clinically important difference in the rate of uterine perforation between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=197; RR=2.97 [95% CI 0.12, 72.03]; low quality); however, there was uncertainty around the estimate.

Important outcomes

Pre-operative expulsion

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence did not detect a clinically important difference in the rate of pre-operative expulsion between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=199; RR=2.97 [95% CI 0.12, 72.05]; low quality); however, there was uncertainty around the estimate.

Ease of procedure – rated as difficult/very difficult

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence showed a higher clinically important difference in the rate of physicians rating the procedure as 'difficult/very difficult' in the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) compared with the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=197; RR=3.63 [95% CI 1.04, 12.61]; moderate quality).

Patient acceptability – satisfied/very satisfied with priming

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence showed there was no clinically important difference between the rate of satisfaction with priming in the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=199; RR=0.99 [95% CI 0.86, 1.14]; high quality).

Patient acceptability – dissatisfied/very dissatisfied with priming

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence did not detect a clinically important difference in the rate of dissatisfaction with priming between the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=199; RR=0.99 [95% CI 0.25, 3.85]; low quality); however, there was uncertainty around the estimate.

Duration of procedure (minutes) – first instrument in to last instrument out

Osmotic dilators + buccal misoprostol + mifepristone versus osmotic dilators + buccal misoprostol (± placebo)

RCT evidence did not detect a clinically important difference in duration of procedure between the 'osmotic dilators + buccal misoprostol + mifepristone' group (misoprostol 400mcg; 1.5 hours before termination; mifepristone 200mg; 24 hours before termination) and the 'osmotic dilators + buccal misoprostol (± placebo)' group (1 RCT, n=45; MD=0.94 minutes [95% CI -2.16, 4.04]; moderate quality); however, there was uncertainty around the estimate.

Osmotic dilators + buccal misoprostol versus osmotic dilators + mifepristone

RCT evidence showed there was no clinically important difference between duration of procedure in the 'osmotic dilators + buccal misoprostol' group (400mcg; 3 hours before termination) and the 'osmotic dilators + mifepristone' group (200mg; 24 hours before termination) (1 RCT, n=196; MD=0.75 minutes [95% CI -0.33, 1.83]; high quality).

Comparison 4. Overnight osmotic dilators versus same-day osmotic dilators

Important outcomes

Baseline cervical dilation

RCT evidence showed a higher clinically important difference in baseline cervical dilation in the 'overnight osmotic dilators' group compared with the 'same-day osmotic dilators' group (1 RCT, n=69; MD=11.7mm [95% CI 6.66, 16.74]; high quality).

Cervical trauma

RCT evidence did not detect a clinically important difference in the rate of cervical trauma between the 'overnight osmotic dilators' group and the 'same-day osmotic dilators' group (1 RCT, n=69; RR=2.92 [95% CI 0.12, 69.20]; low quality); however, there was uncertainty around the estimate.

Uterine perforation

No evidence was identified to inform this outcome.

Important outcomes

Pre-operative expulsion

No evidence was identified to inform this outcome.

Ease of procedure – rated as inadequate dilation

RCT evidence showed a lower clinically important difference in the rate of physicians rating baseline cervical dilation as inadequate in the 'overnight osmotic dilators' group and the 'same-day osmotic dilators' group (1 RCT, n=62; RR=0.39 [95% CI 0.19, 0.80]; high quality).

Patient acceptability – satisfied with termination

RCT evidence did not detect a clinically important difference in the rate of satisfaction with the termination between the 'overnight osmotic dilators' group and the 'same-day osmotic dilators' group (1 RCT, n=67; RR=0.95 [95% CI 0.72, 1.26]; low quality); however, there was uncertainty around the estimate.

Patient acceptability – satisfied with overall clinic experience

RCT evidence did not detect a clinically important difference in the rate of satisfaction with the overall clinic experience between the 'overnight osmotic dilators' group and the 'same-day osmotic dilators' group (1 RCT, n=67; RR=0.91 [95% CI 0.66, 1.24]; moderate quality); however, there was uncertainty around the estimate.

Duration of procedure (minutes) – first instrument in to last instrument out

RCT evidence did not detect a clinically important difference in duration of procedure between the 'overnight osmotic dilators' group and the 'same-day osmotic dilators' group in women of mixed parity (1 RCT, n=69; MD=-2.2 minutes [95% CI -4.28, -0.12]; moderate quality) or nulliparous women (1 RCT, n=21; MD=-5.00 minutes [95% CI -10.53, 0.53]; moderate quality); however, there was uncertainty around the estimates.

Comparison 5. Sublingual misoprostol versus vaginal misoprostol (both 600mcg misoprostol 1.5-2.5 hours before termination; 200mg mifepristone 28 hours before termination)

Critical outcomes

Baseline cervical dilation

Sublingual misoprostol + mifepristone versus vaginal misoprostol + mifepristone

RCT evidence showed there was no clinically important difference between baseline cervical dilation in the 'sublingual misoprostol + mifepristone' group and the 'vaginal misoprostol + mifepristone' group (1 RCT, n=441; MD=0.2mm [95% CI -0.32, 0.72]; moderate quality).

Sublingual misoprostol versus vaginal misoprostol

RCT evidence showed there was no clinically important difference between baseline cervical dilation in the 'sublingual misoprostol' and the 'vaginal misoprostol' group (1 RCT, n=436; MD=0.8mm [95% CI 0.21, 1.39]; moderate quality).

Cervical trauma

No evidence was identified to inform this outcome.

Uterine perforation

No evidence was identified to inform this outcome.

Important outcomes

Pre-operative expulsion

Sublingual misoprostol + mifepristone versus vaginal misoprostol + mifepristone

RCT evidence did not detect a clinically important difference in the rate of pre-operative expulsion between the 'sublingual misoprostol + mifepristone' group and the 'vaginal misoprostol + mifepristone' group (1 RCT, n=450; RR=1.43 [95% CI 0.55, 3.69]; very low quality); however, there was uncertainty around the estimate.

Sublingual misoprostol versus vaginal misoprostol

RCT evidence did not detect a clinically important difference in the rate of pre-operative expulsion between the 'sublingual misoprostol' group and the 'vaginal misoprostol' group (1

RCT, n=450; RR=0.50 [95% CI 0.05, 5.47]; very low quality); however, there was uncertainty around the estimate.

Ease of procedure

No evidence was identified to inform this outcome.

Patient acceptability

No evidence was identified to inform this outcome.

Duration of procedure (minutes) – anaesthesia administered to speculum out

Sublingual misoprostol + mifepristone versus vaginal misoprostol + mifepristone

RCT evidence showed there was no clinically important difference between duration of procedure in the 'sublingual misoprostol + mifepristone' group and the 'vaginal misoprostol + mifepristone' group (1 RCT, n=441; MD=-0.40 minutes [95% CI -1.27, 0.47]; moderate quality).

Sublingual misoprostol versus vaginal misoprostol

RCT evidence showed there was no clinically important difference between duration of procedure in the 'sublingual misoprostol' group and the 'vaginal misoprostol' group (1 RCT, n=436; MD=0.00 minutes [95% CI -1.08, 1.08]; moderate quality).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of cervical priming is to soften and dilate the cervix to facilitate termination of pregnancy; therefore, baseline cervical dilation was selected as a critical outcome to assess the efficacy of priming. The committee agreed that although cervical trauma and uterine perforation are rare in women undergoing surgical termination of pregnancy, they should be prioritised as critical outcomes given the seriousness of such events.

Pre-operative expulsion, which can be very distressing, was selected as an important outcome to allow a balance between benefits and harms of priming to be made as the likelihood of expulsion increases with the addition of priming agents, higher doses and a longer interval between priming agent and termination. Ease and duration of procedure were selected as important outcomes because they are likely to be affected by the adequacy of priming and be related to the risk of complications; further, they may have an impact on physician performance and waiting times for services. Finally, patient acceptability was selected as an important outcome as some priming methods may be considered more acceptable than others due to side effects such as pre-operative pain and bleeding.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology. There was indirect evidence due to some studies including women with gestational ages from 12^{+0} weeks which affected the quality of all outcomes. Evidence for baseline cervical dilation ranged from very low to high quality but the majority of the evidence was of moderate to high quality; the main reason evidence for this outcome was downgraded was due to inconsistency across studies and imprecision due to wide confidence intervals. Uterine perforation, cervical trauma, and pre-operative expulsion are very rare events and the included studies were underpowered to detect their occurrence; therefore, the evidence was

generally low quality (range from very low to moderate) due to imprecision caused by low, and in many cases no, events of interest. Evidence for ease of procedure and patient acceptability ranged from very low to high quality; the main reason evidence was downgraded was due to imprecision and risk of bias due to the objective nature of these outcomes and lack of blinding in included studies. Finally, evidence for duration of procedure ranged from low to high quality; the main reason evidence for this outcome was downgraded was imprecision due to wide confidence intervals.

There was very little evidence comparing osmotic dilators given on the same-day compared with those given the day before termination and very little evidence regarding the optimal regimen for misoprostol and mifepristone used in combination, particularly regarding timing of medication.

Benefits and harms

There was evidence of increased baseline cervical dilation and procedures being rated as 'not difficult', but a decrease in patient acceptability in priming regimens that included osmotic dilators compared with those that used mifepristone and misoprostol, either alone or in combination. Further, there was good evidence of increased baseline cervical dilation when osmotic dilators were inserted the day prior to termination compared with same-day insertion, suggesting that insertion on the same-day allows insufficient time for adequate dilation. However, it was unclear whether or not there was significant differences in patient acceptability, procedure duration or cervical trauma, and no evidence for uterine rupture or pre-operative expulsion. Further, needing to attend another appointment the day before the termination to insert osmotic dilators will increase the burden and duration of treatment for women and place additional demand on services. The committee were unsure whether the benefits of inserting osmotic dilators the day before the termination, compared with the same-day, would outweigh the negative impact this may have on women and services. They agreed that osmotic dilators inserted the day before the termination are more likely to be needed as gestational age advances, but there was not any evidence available beyond 17^{+6} weeks' gestation to inform recommendations. Therefore, the committee recommended that osmotic dilators are offered for cervical priming for women with gestational age greater than or equal to 14^{+0} weeks and that clinicians consider whether or not to insert them the day before the termination. The committee agreed that further research comparing the timing of osmotic dilator insertion would be beneficial to inform future practice so they made a research recommendation (see Appendix L).

The committee made a strong recommendation that misoprostol should not be given as an adjunctive priming agent to osmotic dilators inserted the day before the termination as there was moderate quality evidence showing that there is no increase in baseline cervical dilation when osmotic dilators and misoprostol were given for priming compared with osmotic dilators alone. It was unclear whether or not there were differences in cervical trauma, uterine perforation and pre-operative expulsion when the combination of misoprostol and dilators were used, compared to dilators alone; however, it is feasible that the risk of pre-operative expulsion may increase with additional cervical priming. Further, the use of misoprostol as an adjunct to dilators may have additional side effects, such as gastrointestinal issues depending on route of administration, or may worsen side effects such as pain and bleeding. There was also good evidence that osmotic dilators and misoprostol were not as effective as osmotic dilators and mifepristone.

The committee recommended that mifepristone was considered as an adjunct to osmotic dilators for women beyond 19^{+0} weeks' gestational age as there was evidence of decreased procedural difficulty when osmotic dilators and mifepristone were used for priming compared with osmotic dilators alone. The committee made this a weaker recommendation as it was unclear whether or not there were significant difference in terms of cervical trauma or uterine perforation. However, they noted that the included studies were underpowered to detect differences in these outcomes and therefore agreed a recommendation was warranted. The

combination regimen was only recommended after 19^{+0} weeks' gestation as most of the evidence for combination regimens only included women beyond this time point; recommending combination treatment prior to this point would likely be over-treatment as procedure difficulty increases with gestational age.

There was evidence of decreased patient acceptability with osmotic dilators, so the committee recommended that mifepristone or misoprostol are considered as alternatives as there was evidence of greater acceptability of these methods compared to dilators and, when considering evidence for single priming agents, there were either no differences or unclear differences between dilators and mifepristone or misoprostol in terms of duration of procedure, and it was unclear whether or not there were clinically important differences in cervical trauma, uterine perforation and pre-operative expulsion. Additionally, misoprostol alone either achieved equivalent baseline cervical dilation to osmotic dilators alone, or it was unclear whether or not there were clinically important differences, and it was unclear whether or not there were differences in ease of procedure between mifepristone alone and osmotic dilators alone. If using mifepristone, the committee recommended that 200mg oral mifepristone be given 24 hours before termination for women between 14^{+0} and 16^{+0} weeks' gestational age. All of the studies included in the evidence review used 200mg oral mifepristone, which is standard clinical practice and the majority of studies administered mifepristone 24 hours before the termination. Mifepristone alone was not recommended after 16^{+0} weeks' gestation as there was no evidence available beyond this time point. If using misoprostol, the committee recommended that buccal, vaginal or sublingual misoprostol be given for women between 14^{+0} and 19^{+0} weeks' gestational age. Oral misoprostol was not considered appropriate due to longer absorption time and greater side effects compared with other routes of misoprostol administration and therefore was not included in the review protocol for this question. Insufficient evidence was available to specify a dose of misoprostol; there was some evidence of greater baseline dilation with 600mcg compared with 400mcg misoprostol but there was no direct comparison and it was not possible to separate the effect of dose and interval. There was also insufficient evidence to specify the interval between misoprostol and termination, as there was no direct comparison between different intervals and the interval used in included studies ranged from 1 hour to greater than 6 hours. Misoprostol alone was not recommended after 19^{+0} weeks' gestation as there was no evidence available beyond this time point. The committee acknowledged that there was no evidence on the effectiveness of mifepristone or misoprostol compared with osmotic dilators after 19^{+0} weeks' gestation; therefore, it was not possible to recommend an alternative to osmotic dilators from 19^{+1} weeks' gestation as effectiveness is not known. The committee agreed that further research on the effectiveness of pharmacologic agents for cervical priming beyond 16^{+0} weeks' gestation would be beneficial to inform future practice, specifically whether they are acceptable alternatives to osmotic dilators; therefore, they made a research recommendation (see Appendix L).

There was very limited evidence for the efficacy of mifepristone given 24 hours prior to termination in combination with misoprostol compared with other cervical priming regimens. However, there is evidence that that when mifepristone was given 2 days prior to the termination, and 48 hours before misoprostol, there were a greater number of pre-operative expulsions. The committee agreed that the evidence was not strong enough to recommend that mifepristone and misoprostol should not be given in combination due to the insufficient evidence of misoprostol and mifepristone used in combination when mifepristone was given at the recommended interval of 24 hours before termination; further, the evidence of a greater pre-operative expulsion rate came from a study (Carbonell 2007) that inserted osmotic dilators (at the physicians discretion) at the time of misoprostol if dilation was considered inadequate, which may have contributed to the greater pre-operative expulsion rate. Finally, the committee agreed that, mifepristone and misoprostol may be the only viable option at advanced gestational ages if there is not someone skilled available to place osmotic dilators.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed the potential costs and savings of recommendations and thought that there would not be a substantial increase in costs as the number of women having a surgical termination during the second trimester is small. Further, as it is current practice to give cervical priming for all women after 14^{+0} weeks' gestation and combination regimens were only recommended after 19^{+0} weeks' gestation, there is unlikely to be increased costs associated with cost of priming agents.

However, these recommendations will lead to a greater use of osmotic dilators, and may increase the number that are inserted the day before, requiring a greater number of women to attend an appointment the day before the termination. This will require additional resources and increase costs, particularly as osmotic dilators have to be placed by a skilled clinician. There may also be an increase in costs associated with hotel accommodation needed for women travelling for a termination where this cost is covered by the termination service rather than the women.

Other considerations

The use of cervical priming agents compared with no priming agent was not considered as part of this review question as using a preparatory agent to achieve dilation prior to surgical termination in the second trimester is the standard of care and recommended in the Royal College of Obstetricians and Gynaecologists (2011) guideline on termination of pregnancy. However, the committee agreed that cervical priming should be for all women between 14^{+0} and 13^{+6} weeks' gestation.

The committee were aware that in a number of the included studies, additional doses of misoprostol or mifepristone were given prior to termination if, upon inspection, insufficient baseline dilation had occurred during the time allotted for cervical priming. Therefore, the doses specified in the recommendations correspond to the initial doses that should be given for each agent. It was not possible to make recommendations on any additional cervical priming that should be given if insufficient dilation has occurred, or at what time point this should be reviewed, as this was not included in the review protocol; however, the committee acknowledged that further doses of misoprostol or mifepristone may be given if required.

Finally, the committee were aware of RCT evidence showing reduced pain and increased patient satisfaction with insertion of laminaria under a paracervical block with lidocaine and sodium bicarbonate compared with when a sham block was used (Soon 2017). Further, the majority of the studies included in this evidence review used a paracervical block prior to the insertion of dilators. Therefore, the committee considered it appropriate to use a paracervical block when using osmotic dilators for cervical priming. However, they were unable to make recommendations in this area as the use of analgesia and anaesthetic for the insertion of osmotic dilators was not considered as part of this review question.

The evidence considered for this review question covered the gestational age range between 14^{+0} and 24^{+0} weeks' gestation. However, recommendations were made for women between 14^{+0} and 23^{+6} weeks' gestation to be consistent with the requirements of the 1967 Abortion Act.

References

Ashok 2000

Ashok, P. W., Flett, G. M., Templeton, A. (2000). Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study. American Journal of Obstetrics & Gynecology, 183, 998-1002.

Boraas 2016

Boraas, C. M., Achilles, S. L., Cremer, M. L., Chappell, C. A., Lim, S. E., Chen, B. A. (2016) Synthetic osmotic dilators with adjunctive misoprostol for same-day dilation and evacuation: a randomized controlled trial. Contraception, 94, 467-472.

Borgatta 2012

Borgatta, L., Roncari, D., Sonalkar, S., Mark, A., Hou, M.Y., Finneseth, M., Vragovic, O. (2012) Mifepristone vs. osmotic dilator insertion for cervical preparation prior to surgical abortion at 14-16 weeks: a randomized trial. Contraception, 86, 567-571.

Cakir 2005

Cakir, L., Dilbaz, B., Caliskan, E., Dede, F. S., Dilbaz, S., Haberal, A. (2005). Comparison of oral and vaginal misoprostol for cervical ripening before manual vacuum aspiration of first trimester pregnancy under local anesthesia: A randomized placebo-controlled study. Contraception, 71, 337-342.

Carbonell Esteve 2006

Carbonell Esteve, J. L., Mari, J. M., Valero, F., Llorente, M., Salvador, I., Varela, L., Leal, P., Candel, A., Tudela, A., Serrano, M., Munoz, E. (2006). Sublingual versus vaginal misoprostol (400 microg) for cervical priming in first-trimester abortion: a randomized trial. Contraception, 74, 328-33.

Carbonell 2007

Carbonell, J. L., Gallego, F. G., Llorente, M. P., Bermudez, S. B., Sala, E. S., Gonzalez, L. V., Texido, C. S. (2007) Vaginal vs. sublingual misoprostol with mifepristone for cervical priming in second-trimester abortion by dilation and evacuation: a randomized clinical trial. Contraception, 75, 230-7.

Casey 2016

Casey, F. E., Ye, P. P., Perritt, J. D., Moreno-Ruiz, N. L., Reeves, M. F. (2016) A randomized controlled trial evaluating same-day mifepristone and misoprostol compared to misoprostol alone for cervical preparation prior to second-trimester surgical abortion. Contraception, 94, 127-33.

Chitaishvili 2007

Chitaishvili, D., Asatiani, T. (2007). Sublingual misoprostol prior to manual vacuum aspiration for reducing blood loss at 8-12 weeks of gestation: a randomized double-blind placebo-controlled study. Georgian Medical News, 26-30.

de Jonge 2000

de Jonge, E. T., Jewkes, R., Levin, J., Rees, H. (2000). Randomised controlled trial of the efficacy of misoprostol used as a cervical ripening agent prior to termination of pregnancy in the first trimester. South African Medical Journal, 90, 256-62.

Drey 2014

Drey, E. A., Benson, L. S., Sokoloff, A., Steinauer, J. E., Roy, G., Jackson, R. A. (2014) Buccal misoprostol plus laminaria for cervical preparation before dilation and evacuation at 21-23 weeks of gestation: A randomized controlled trial. Contraception, 89, 307-313.

Edelman 2006

Edelman, A. B., Buckmaster, J. G., Goetsch, M. F., Nichols, M. D., Jensen, J. T. (2006) Cervical preparation using laminaria with adjunctive buccal misoprostol before second-trimester dilation and evacuation procedures: a randomized clinical trial. American Journal of Obstetrics & Gynecology, 194, 425-30.

Goldberg 2005

Goldberg, A. B., Drey, E. A., Whitaker, A. K., Kang, M. S., Meckstroth, K. R., Darney, P. D. (2005). Misoprostol compared with laminaria before early second-trimester surgical abortion: a randomized trial. Obstetrics & Gynecology, 106, 234-41.

Goldberg 2015

Goldberg, A. B., Fortin, J. A., Drey, E. A., Dean, G., Lichtenberg, E. S., Bednarek, P. H., Chen, B. A., Dutton, C., McKetta, S., Maurer, R., Winikoff, B., Fitzmaurice, G. M. (2015). Cervical Preparation before Dilation and Evacuation Using Adjunctive Misoprostol or Mifepristone Compared With Overnight Osmotic Dilators Alone: A Randomized Controlled Trial. Obstetrics & Gynecology, 126, 599-609.

Grossman 2014

Grossman, D., Constant, D., Lince-Deroche, N., Harries, J., Kluge, J. (2014) A randomized trial of misoprostol versus laminaria before dilation and evacuation in South Africa. Contraception, 90, 234-41.

Inal 2003

Inal, M.M., Ertopcu, K., Arici, A., Ozelmas, I. (2003). The effect of oral versus vaginal misoprostol on cervical dilatation in first-trimester abortion: a double-blind, randomized study. European Journal of Contraception and Reproductive Health Care, 8, 197-202.

Li 2003

Li, C. F., Chan, C. W., Ho, P. C. (2003). A comparison of isosorbide mononitrate and misoprostol cervical ripening before suction evacuation. Obstetrics & Gynecology, 102, 583-8.

Meirik 2012

Meirik, O., My Huong, N. T., Piaggio, G., Bergel, E., von Hertzen, H., W. H. O. Research Group on Postovulatory Methods of Fertility Regulation. (2012). Complications of first-trimester abortion by vacuum aspiration after cervical preparation with and without misoprostol: a multicentre randomised trial. Lancet, 379, 1817-24.

Newmann 2014

Newmann, S. J., Sokoloff, A., Tharyil, M., Illangasekare, T., Steinauer, J. E., Drey, E. A. (2014) Same-day synthetic osmotic dilators compared with overnight laminaria before abortion at 14-18 weeks of gestation: a randomized controlled trial. Obstetrics & Gynecology, 123, 271-8.

RCOG 2011

Royal College of Obstetricians and Gynaecologists. (2011). The Care of Women Requesting Induced Abortion (Evidence-based Clinical Guideline No. 7).

Saav 2015

Saav, I., Kopp Kallner, H., Fiala, C., Gemzell-Danielsson, K. (2015). Sublingual versus vaginal misoprostol for cervical dilatation 1 or 3 h prior to surgical abortion: a double-blinded RCT. Human Reproduction, 30, 1314-22.

Saxena 2003

Saxena, P., Salhan, S., Sarda, N. (2003). Role of sublingual misoprostol for cervical ripening prior to vacuum aspiration in first trimester interruption of pregnancy. Contraception, 67, 213-217.

Saxena 2006

Saxena, P., Salhan, S., Sarda, N. (2006). Sublingual versus vaginal route of misoprostol for cervical ripening prior to surgical termination of first trimester abortions. European Journal of Obstetrics, Gynecology, & Reproductive Biology, 125, 109-13.

Saxena 2008

Saxena, P., Sarda, N., Salhan, S., Nandan, D. (2008). A randomised comparison between sublingual, oral and vaginal route of misoprostol for pre-abortion cervical ripening in first-trimester pregnancy termination under local anaesthesia. Australian & New Zealand Journal of Obstetrics & Gynaecology, 48, 101-6.

Sagiv 2015

Sagiv, R., Mizrachi, Y., Glickman, H., Kerner, R., Keidar, R., Bar, J., Golan, A. (2015) Laminaria vs. vaginal misoprostol for cervical preparation before second-trimester surgical abortion: a randomized clinical trial. Contraception, 91, 406-11.

Shaw 2015

Shaw, K. A., Shaw, J. G., Hugin, M., Velasquez, G., Hopkins, F. W., Blumenthal, P. D. (2015) Adjunct mifepristone for cervical preparation prior to dilation and evacuation: a randomized trial. Contraception, 91, 313-9.

Shaw 2017

Shaw, K. A., Lerma, K., Shaw, J. G., Scrivner, K. J., Hugin, M., Hopkins, F. W., Blumenthal, P. D. (2017). Preoperative effects of mifepristone for dilation and evacuation after 19 weeks of gestation: a randomised controlled trial. 124, 1973-1981.

Soon 2017

Soon, R., Tschann, M., Salcedo, J., Stevens, K., Ahn, H. J., Kaneshiro, B. (2017). Paracervical block for Laminaria insertion before second-trimester abortion: A randomised controlled trial. Obstetrics & Gynaecology, 130, 387-392

Sharma 2005

Sharma, S., Refaey, H., Stafford, M., Purkayastha, S., Parry, M., Axby, H. (2005). Oral versus vaginal misoprostol administered one hour before surgical termination of pregnancy: a randomised controlled trial. British Journal of Obstetrics and Gynaecology, 112, 456-60.

Sharma 2011

Sharma, M. (2011). Sublingual misoprostol for cervical priming in surgical first trimester pregnancy termination. Journal of Obstetrics & Gynaecology of India, 61, 531-3.

Tang 2004

Tang, O. S., Mok, K. H., Ho, P. C. (2004). A randomized study comparing the use of sublingual to vaginal misoprostol for pre-operative cervical priming prior to surgical termination of pregnancy in the first trimester. Human Reproduction, 19, 1101-4.

Vimala 2003

Vimala, N., Mittal, S., Kumar, S. (2003). Sublingual misoprostol for preabortion cervical ripening in first-trimester pregnancy termination. Contraception, 67, 295-297.

Vimala 2004a

Vimala, N., Mittal, S., Kumar, S., Dadhwal, V., Sharma, Y. (2004a) A randomized comparison of sublingual and vaginal misoprostol for cervical priming before suction termination of first-trimester pregnancy. Contraception, 70, 117-120.

Vimala 2004b

Vimala, N., Mittal, S., Kumar, S. (2004b). Sublingual misoprostol before first trimester abortion: a comparative study using two dose regimens. Indian Journal of Medical Sciences, 58, 54-61.

Appendices

Appendix A – Review protocols

Review protocol for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy in the first trimester?
Review question in guideline	What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation?
Type of review question	Intervention
Objective of the review	To determine the optimal cervical priming regimen (if any) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation
Eligibility criteria – population	Women who are having surgical termination of pregnancy up to and including 13^{+6} weeks' gestation. Exclusions: - Studies with indirect populations will not be considered
Eligibility criteria – intervention(s)	Cervical priming agent: • Mifepristone (oral) • Misoprostol (vaginal, sublingual, buccal)
Eligibility criteria – comparator(s)	1. Cervical priming agent versus placebo or no agent 2. Cervical priming agent A versus cervical priming agent B 3. Cervical priming agent A – dose A versus cervical priming agent A – dose B 4. Cervical priming agent A – interval A versus cervical priming agent A – interval B 5. Misoprostol route A versus misoprostol route B
Outcomes and prioritisation	**Critical outcomes:** • Incomplete abortion (need for re-evacuation or re-aspiration) • Cervical trauma • Uterine perforation

Field (based on PRISMA-P	Content
	Important outcomes: • Ease of cervical dilation/force required to dilate (e.g., measured by tonometer) • Pre-operative pain using patient reported pain score/validated pain scales • Pre-operative expulsion of fetus • Pre-operative bleeding
Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs
Other inclusion exclusion criteria	Inclusion: - English-language - Studies conducted from 2000 (see below)
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Medical conditions: - Complex pre-existing medical conditions - No complex pre-existing medical conditions Parity: - Nulliparous - Parous Age: - <18 years old - ≥18 years old Gestation: - <9 weeks - ≥9 to 13^{+6}
Selection process – duplicate screening/selection/analysis	Dual weeding will not be performed for this question Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design):

Field (based on PRISMA-P	Content
	Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews Dates: from 2000 Studies conducted from 2000 will be considered for this review question, as the first RCOG guidance on termination of pregnancy was published in 2000 and was followed by substantial changes in practice
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables)
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all other outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter Minimally important differences: For all outcomes default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P	Content
	If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Profession Iain Cameron in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance will undertake systematic literature searches, appraise the evidence, conduct meta-analysis and cost-effectiveness analysis where appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

GRADE: Grading of Recommendations Assessment, Development and Evaluation; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCOG: Royal College of Obstetricians and Gynaecologists; RCT: randomised controlled trial; RoBIS: risk of bias in systematic reviews; SD: standard deviation

Review protocol for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24+0 weeks' gestation?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the optimal regimen for cervical priming before surgical termination of pregnancy in the second trimester?
Review question in guideline	What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?
Type of review question	Intervention
Objective of the review	To determine the optimal cervical priming regimen (if any) before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation

Field (based on PRISMA-P	Content
Eligibility criteria – population	Women who are having surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation. Exclusions: - Studies with indirect populations will not be considered
Eligibility criteria – intervention(s)	Cervical priming agent: • Mifepristone (oral) • Misoprostol (oral, vaginal, sublingual, buccal) • Osmotic cervical dilators
Eligibility criteria – comparator(s)	1. Cervical priming agent A versus cervical priming agent B 2. Cervical priming agents (combination of any 2 or 3) versus cervical priming agent (single) 3. Cervical priming agents (combination of any 2 or 3) versus cervical priming agents (combination of any 2 or 3) 4. Cervical priming agent A – dose A versus cervical priming agent A – dose B 5. Cervical priming agent A – interval A versus cervical priming agent A – interval B 6. Misoprostol route A versus misoprostol route B
Outcomes and prioritisation	**Critical outcomes:** • Baseline cervical dilation • Cervical trauma • Uterine perforation **Important outcomes:** • Pre-operative expulsion • Ease of procedure (measured using a Likert scale) • Patient acceptability • Duration of procedure
Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs
Other inclusion exclusion criteria	Inclusion: - English-language - Studies conducted from 1985 (see below)
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Medical conditions: - Complex pre-existing medical conditions

Field (based on PRISMA-P	Content
	- No complex pre-existing medical conditions Age: - <18 years old - ≥18 years old Parity: - Nulliparous - Parous Previous births: - Previous caesarean section - No previous caesarean section
Selection process – duplicate screening/selection/analysis	Dual weeding will not be performed for this question Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews Dates: from 1985 Studies conducted from 1985 onwards will be considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991.
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D

Field (based on PRISMA-P	Content
	(clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all other outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter Minimally important differences: Procedure duration: 3 minutes Baseline dilation: 2 dilator sizes (equivalent to 4mm if using French sized dilators) For all other outcomes default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Profession Iain Cameron in line with section 3 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P	Content
	Staff from The National Guideline Alliance will undertake systematic literature searches, appraise the evidence, conduct meta-analysis and cost-effectiveness analysis where appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

GRADE: Grading of Recommendations Assessment, Development and Evaluation; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RoBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategy for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation?

Literature search strategy for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

The search for this topic was last run on 19th November 2018 during the re-runs for this guideline.

Database: Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2018 November 16, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to November 16, 2018
Date of last search: 19th November 2018

#	Searches
1	exp abortion/ use emczd
2	exp pregnancy termination/ use emczd
3	exp Abortion, Induced/ use ppez
4	Abortion Applicants/ use ppez
5	exp Abortion, Spontaneous/ use ppez
6	exp Abortion, Criminal/ use ppez
7	Aborted fetus/ use ppez
8	fetus death/ use emczd
9	abortion.mp.
10	(abort$ or postabort$ or preabort$).tw.
11	((f?etal$ or f?etus$ or gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) and terminat$).tw.
12	((f?etal$ or f?etus$) adj loss$).tw.
13	((gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) adj3 loss$).tw.
14	(((elective$ or threaten$ or voluntar$) adj3 interrupt$) and pregnan$).tw.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Cervical Ripening/ use ppez
17	uterine cervix ripening/ use emczd
18	((cervi$ or intracervi$ or intra-cervi$ or mifepriston$ or misoprostol) adj5 (priming or ripen$ or soften$ or dilat$ or prepar$ or maturat$)).mp.
19	osmotic cervical dilator/ use emczd
20	exp uterine cervix dilatation/ use emczd
21	(osmotic adj5 dilator$).mp.
22	(laminaria$ or dilapan$ or lamicel$).mp.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23
25	limit 24 to english language
26	limit 25 to yr="1985 -Current"
27	Limit 26 to RCTs and SRs, and general exclusions filter applied

#	Searches
28	remove duplicates from 27

Database: Cochrane Library via Wiley Online
Date of last search: 19th November 2018

#	Searches
#1	MeSH descriptor: [Abortion, Induced] explode all trees
#2	MeSH descriptor: [Abortion Applicants] explode all trees
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)
#8	((fetal* or fetus* or foetal* or foetus* or gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) and terminat*):ti,ab,kw (Word variations have been searched)
#9	((fetal* or fetus* or foetal* or foetus*) next loss*):ti,ab,kw (Word variations have been searched)
#10	((gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) near/3 loss*):ti,ab,kw (Word variations have been searched)
#11	(((elective* or threaten* or voluntar*) near/3 interrupt*) and pregnan*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Cervical Ripening] this term only
#14	((cervi* or intracervi* or intra-cervi* or mifepriston* or misoprostol) near/5 (priming or ripen* or soften* or dilat* or prepar* or maturat*)):ti,ab,kw (Word variations have been searched)
#15	(osmotic near/5 dilator*):ti,ab,kw (Word variations have been searched)
#16	(laminaria* or dilapan* or lamicel*):ti,ab,kw (Word variations have been searched)
#17	#13 or #14 or #15 or #16
#18	#12 and #17 Publication Year from 1985 to 2018

Literature search strategy for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation?

Literature search strategy for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

The search for this topic was last run on 19th November 2018 during the re-runs for this guideline.

Database: Medline & Embase (Multifile)

Last searched on **Embase Classic+Embase** 1947 to 2018 November 16, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to November 16, 2018

Date of last search: 19th November 2018

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2	exp pregnancy termination/ use emczd
3	exp Abortion, Induced/ use ppez
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5	exp Abortion, Spontaneous/ use ppez
6	exp Abortion, Criminal/ use ppez
7	Aborted fetus/ use ppez
8	fetus death/ use emczd
9	abortion.mp.
10	(abort$ or postabort$ or preabort$).tw.
11	((f?etal$ or f?etus$ or gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) and terminat$).tw.
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13	((gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) adj3 loss$).tw.
14	(((elective$ or threaten$ or voluntar$) adj3 interrupt$) and pregnan$).tw.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Cervical Ripening/ use ppez
17	uterine cervix ripening/ use emczd
18	((cervi$ or intracervi$ or intra-cervi$ or mifepriston$ or misoprostol) adj5 (priming or ripen$ or soften$ or dilat$ or prepar$ or maturat$)).mp.
19	osmotic cervical dilator/ use emczd
20	exp uterine cervix dilatation/ use emczd
21	(osmotic adj5 dilator$).mp.
22	(laminaria$ or dilapan$ or lamicel$).mp.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23
25	limit 24 to english language
26	limit 25 to yr="1985 -Current"
27	Limit 26 to RCTs and SRs, and general exclusions filter applied
28	remove duplicates from 27

Database: Cochrane Library via Wiley Online

Date of last search: 19th November 2018

#	Searches
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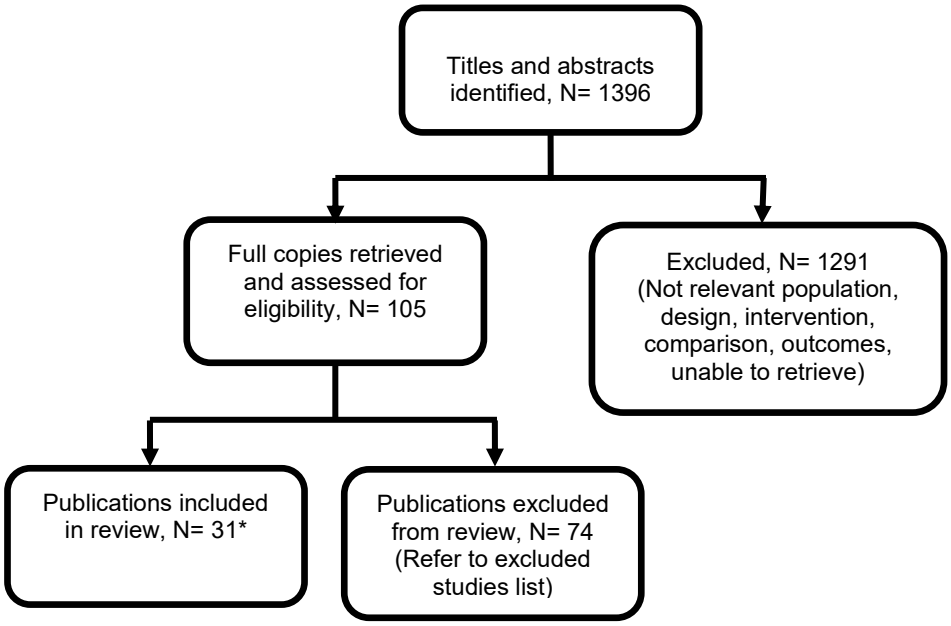
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)
#8	((fetal* or fetus* or foetal* or foetus* or gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) and terminat*):ti,ab,kw (Word variations have been searched)
#9	((fetal* or fetus* or foetal* or foetus*) next loss*):ti,ab,kw (Word variations have been searched)
#10	((gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) near/3 loss*):ti,ab,kw (Word variations have been searched)
#11	(((elective* or threaten* or voluntar*) near/3 interrupt*) and pregnan*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Cervical Ripening] this term only
#14	((cervi* or intracervi* or intra-cervi* or mifepriston* or misoprostol) near/5 (priming or ripen* or soften* or dilat* or prepar* or maturat*)):ti,ab,kw (Word variations have been searched)
#15	(osmotic near/5 dilator*):ti,ab,kw (Word variations have been searched)
#16	(laminaria* or dilapan* or lamicel*):ti,ab,kw (Word variations have been searched)
#17	#13 or #14 or #15 or #16
#18	#12 and #17 Publication Year from 1985 to 2018

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

Clinical evidence study selection for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

*Figure **1**: Study selection flow chart*



Literature search and study selection undertaken for both cervical priming questions simultaneously; 18 publications were included for cervical priming up to 13^{+6} weeks' gestation and 13 publications were included for cervical priming between 14^{+0} and 24^{+0} weeks' gestation

Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Ashok, P. W., Flett, G. M., Templeton, A., Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 183, 998-1002, 2000 **Ref Id** 770838 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To compare the cervical priming effect of mifepristone administered at different intervals with that of misoprostol	**Sample size** n=90 randomised (n=30 24h mifepristone; n=30 48h mifepristone; n=30 misoprostol) All treated per protocol and included in analysis **Characteristics** Age in years (median; range reported in parentheses): 24h mifepristone: 23.9 (16.6-35.3) 48h mifepristone: 21.8 (15.0-42.8) Misoprostol: 22.9 (16.1-40.0) Gestational age in weeks (median; range reported in parentheses): 24h mifepristone: 9.0 (7.0-12.1) 48h mifepristone: 9.6 (6.6-11.4) Misoprostol: 9.1 (7.0-11.6) Primigravid (number; percentage in parentheses): 24h mifepristone: 20 (66.7) 48h mifepristone: 19 (63.3) Misoprostol: 18 (60)	All women received a questionnaire at the time the cervical priming agent was administered to assess patient satisfaction and side effects which was collected immediately prior to transfer to surgical suite. Prior to the termination, baseline cervical dilation and the force required to dilate to 9mm was assessed. Further cervical dilation was performed using Hegar dilators as required and the uterus was evacuated using a Karman suction curette. **24h mifepristone:** Women attended the ward 24 hours before the scheduled termination to take 200mg oral mifepristone. **48h mifepristone:** Women attended the ward 48 hours before the	**Outcome: Cumulative force (N) required to dilate cervix (to 9mm)** 24h mifepristone: N=30, M=37.7, SD=28.2 48h mifepristone: N=30, M=23.4, SD=19.0 Misoprostol: N=30, M=40.0, SD=23.4 **Outcome: Pre-operative pain (abdominal)** 24h mifepristone: 16/30 48h mifepristone: 21/30 Misoprostol: 20/29 **Outcome: Pre-operative bleeding:**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: unclear risk, insufficient information reported Allocation concealment: low risk, sequentially numbered sealed opaque envelopes Blinding of participants and personnel: no blinding; low risk for objective outcomes; high risk for subjective outcomes Blinding of outcome assessment: no blinding; low risk for objective outcomes; high risk for subjective outcomes Attrition: low risk for all outcomes; missing data for 1 woman in misoprostol arm because they were not administered questionnaire Selective reporting: low risk, all outcomes reported in sufficient detail for analysis

Study details	Participants	Interventions	Outcomes and Results	Comments
prior to suction termination of pregnancy **Study dates** December 1997 - November 1998 **Source of funding** No sources of funding reported	Prior termination (number; percentage in parentheses): 24h mifepristone: 6 (20) 48h mifepristone: 9 (30) Misoprostol: 11 (36.7) Weight in kg (median; range in parentheses): 24h mifepristone: 60.3 (63.0-120.7) 48h mifepristone: 61.9 (42.0-82.6) Misoprostol: 59.9 (47.6-79.4) **Inclusion criteria** Women between 15 and 40 requesting a surgical termination between 6.6 and 12.1 weeks' gestation who had no contraindications to prostaglandin or mifepristone **Exclusion criteria** Symptoms of threatened miscarriage; history of cervical surgery; lived ≥1 hour away from the hospital; multiple pregnancy	scheduled termination to take 200mg oral mifepristone. **Misoprostol:** Women attended the ward 24 (2 to 4) hours before the scheduled termination and 4 800micrograms (mcg; 4 200mcg) misoprostol tablets were placed in the vaginal fornix by a nurse.	24h mifepristone: 2/30 48h mifepristone: 6/30 Misoprostol: 3/29	**Other information** The abstract and the methods section of this paper reported different misoprostol regimens and no erratum has been published. After discussion with the guideline committee, it was agreed that the likely regimen was 4 200mcg misoprostol tablets 2 to 4 hours before the termination.
Full citation Cakir, L., Dilbaz, B., Caliskan, E., Dede, F. S., Dilbaz, S., Haberal, A., Comparison of oral and vaginal misoprostol for cervical ripening before manual	**Sample size** n=160 randomised (n=40 oral misoprostol [not included in evidence review]; n=40 vaginal misoprostol; n=40 oral placebo	All women underwent an initial vaginal examination and measurement of basal cervical dilation; medical and obstetric history was obtained and gestational age	**Outcome: Pre-operative pain (abdominal)** Vaginal misoprostol: 30/40	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool

Study details	Participants	Interventions	Outcomes and Results	Comments
vacuum aspiration of first trimester pregnancy under local anesthesia: A randomized placebo-controlled study, Contraception, 71, 337-342, 2005 **Ref Id** 771044 **Country/ies where the study was carried out** Turkey **Study type** Randomised controlled trial **Aim of the study** To determine the effectiveness of oral and vaginal misoprostol compared with placebo for cervical priming prior to surgical termination (oral misoprostol not included in evidence review) **Study dates** April 2003 - September 2003 **Source of funding** No sources of funding reported	[not included in evidence review]; n=40 vaginal placebo) All treated per protocol and included in analysis **Characteristics** Age in years (mean; standard deviation in parentheses): Vaginal misoprostol: 30.9 (6.09) Vaginal placebo: 30.3 (5.7) Gestational age in days (mean; standard deviation in parentheses): Vaginal misoprostol: 55.5 (5.3) Vaginal placebo: 55 (4.6) Nulliparous (number; percentage in parentheses): Vaginal misoprostol: 0 (0) Vaginal placebo: 1 (2.5) Primiparous (number; percentage in parentheses): Vaginal misoprostol: 8 (20) Vaginal placebo: 10 (25) Multiparous (number; percentage in parentheses): Vaginal misoprostol: 32 (80) Vaginal placebo: 29 (72.5) Previous termination (number; percentage in parentheses): Vaginal misoprostol: 14 (35) Vaginal placebo: 12 (30)	was confirmed using ultrasound. Women then fasted overnight before the procedure and were admitted and received study medication. After 3 hours, any side effects were recorded and the termination was completed using manual vacuum aspiration with Karman suction curette. All women were observed for 3 hours following the termination and were given doxycycline and paracetamol before discharge. Follow-up occurred 7 to 10 days later to record postoperative bleeding and side effects. **Vaginal misoprostol:** Two misoprostol tablets (total 400mcg) were placed in the vaginal fornix 3 hours before the termination **Vaginal placebo:** Two placebo tablets were placed in the vaginal fornix 3 hours before the termination	Vaginal placebo: 10/40 **Outcome: Pre-operative expulsion** Vaginal misoprostol: 0/40 Vaginal placebo: 0/40 **Outcome: Pre-operative bleeding in ml** Vaginal misoprostol: N=40, M=3.1, SD=0.9 Vaginal placebo: N=40, M=0.2, SD=0.3	Random sequence generation: low risk, computer-generated prepared by independent staff Allocation concealment: unclear risk, randomisation does not appear to have been concealed until after administration of study medications; concealed in sealed envelope by midwife after priming agent was administered Blinding of participants and personnel: low risk, double blind (physician was able to identify remnants of medication as misoprostol for 1 woman) Blinding of outcome assessment: low risk, double blind (physician was able to identify remnants of medication as misoprostol for 1 woman) Attrition: low risk for all outcomes; all women treated per protocol and no loss to follow-up Selective reporting: low risk, all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	BMI kg/m2 (mean; standard deviation in parentheses): Vaginal misoprostol: 25.1 (4.1) Vaginal placebo: 23.9 (3.6) **Inclusion criteria** Women requesting termination of pregnancy between 7 and 10 weeks' gestation **Exclusion criteria** Systemic disease; contraindication to misoprostol; previous cervical operation; bleeding or spotting during current pregnancy or threated/missed spontaneous abortion; multiple pregnancy; basal cervical dilation ≥4mm; preoperative haemoglobin <10g/dl			
Full citation Carbonell Esteve, J. L., Mari, J. M., Valero, F., Llorente, M., Salvador, I., Varela, L., Leal, P., Candel, A., Tudela, A., Serrano, M., Munoz, E., Sublingual versus vaginal misoprostol (400 microg) for cervical priming in first-trimester abortion: a randomized trial, Contraception, 74, 328-33, 2006 **Ref Id**	**Sample size** n=1,430 randomised (n=715 sublingual misoprostol; n=715 vaginal misoprostol) n= 1,424 ITT (n=716 sublingual misoprostol*; n =708 vaginal misoprostol); included in characteristics and side effects n=1,258 per protocol (n=626 sublingual misoprostol [n=65 <1 hour between misoprostol and termination; n=25 >3 between misoprostol and termination];	At the first visit, all women had gestational age confirmed by abdominal or vaginal ultrasound and a blood sample was taken to assess complete blood count, blood type, and Rhesus factor. On the second visit, women received study medications between 1 hour and 3 hours before scheduled termination and women were	**Outcome: Cervical trauma:** Sublingual misoprostol: 0/626 Vaginal misoprostol: 0/632 **Outcome: Uterine perforation:** Sublingual misoprostol: 0/626 Vaginal misoprostol: 0/632	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated (MEDTAT) by independent statistician Allocation concealment: low risk, sequentially numbered sealed

Study details	Participants	Interventions	Outcomes and Results	Comments
386847 **Country/ies where the study was carried out** Spain **Study type** Randomised controlled trial **Aim of the study** To compare the effectiveness and acceptability of sublingual and vaginal misoprostol for cervical priming prior to surgical termination **Study dates** February 2004 - October 2004 **Source of funding** No sources of funding reported	n=632 vaginal misoprostol [n=51 <1 hour between misoprostol and termination; n=25 >3 hour between misoprostol and termination); included in surgical outcomes Note. no account of differences between numbers randomised and numbers in ITT analysis **Characteristics** Age in years (mean; standard deviation in parentheses): Sublingual misoprostol: 26.4 (6.3) Vaginal misoprostol: 27.4 (6.8) Gestational age in days (mean; standard deviation in parentheses): Sublingual misoprostol: 54.8 (13.0) Vaginal misoprostol: 54.6 (13.0) Gravidity (mean; standard deviation in parentheses): Sublingual misoprostol: 2.5 (1.7) Vaginal misoprostol: 2.6 (1.8) Parity (mean; standard deviation in parentheses): Sublingual misoprostol: 1.0 (1.3) Vaginal misoprostol: 1.1 (1.4) Parity ≥1 (number; percentage in parentheses):	administered 50mg intramuscular anti-Rh globulin if there were Rh-negative. Women were examined hourly during the interval between administration of misoprostol and transfer to the operating theatre; the termination was performed by aspiration under guidance of abdominal ultrasound. **Sublingual misoprostol:** Two 200mcg misoprostol tablets were placed under the tongue 1 to 3 hours before termination; women were instructed not to move the tablets **Vaginal misoprostol:** Two moistened 200mcg misoprostol tablets were placed vaginally 1 to 3 hours before termination	**Outcome: Ease of cervical dilation (physician reported):** <u>Not needed:</u> Sublingual misoprostol: 224/626 Vaginal misoprostol: 184/632 <u>Easy:</u> Sublingual misoprostol: 299/626 Vaginal misoprostol: 339/632 <u>Normal:</u> Sublingual misoprostol: 86/626 Vaginal misoprostol: 83/632 <u>Difficult:</u> Sublingual misoprostol: 17/626 Vaginal misoprostol: 26/632	opaque envelopes prepared by independent staff Blinding of participants and personnel: no blinding; low risk for objective outcomes; high risk for subjective outcomes Blinding of outcome assessment: no blinding; low risk for objective outcomes; high risk for subjective outcomes Attrition: unclear risk; reasons people did not participate in study are not reported; high protocol violations (although rates similar between arms) Selective reporting: moderate risk, all outcomes reported in sufficient detail with the exception of incomplete abortion (2 events occurred in vaginal misoprostol arm due to double uterus/uterine septum; 1 additional event occurred due to hematometra but did not report which arm this was in) and intraoperative bleeding (percentages reported based on interval between misoprostol administration and termination but number in these groups is not known) **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	Sublingual misoprostol: 362 (50.6) Vaginal misoprostol: 373 (51.9) Previous terminations (mean; standard deviation in parentheses): Sublingual misoprostol: 0.4 (0.8) Vaginal misoprostol: 0.5 (1.0) Previous caesarean section (mean; standard deviation in parentheses): Sublingual misoprostol: 0.1 (0.4) Vaginal misoprostol: 0.2 (0.3) **Inclusion criteria** Women requesting surgical terminations up to 84 days gestation who were able to give informed consent (written parental/guardian permission required for adolescents) and willing to abstain from intercourse for 14 days following the termination **Exclusion criteria** Haemoglobin <10.0mg/dl; blood pressure ≥160/90mmHg; prior uterine bleeding; active genital infection; suspected or confirmed ectopic pregnancy; contraindication to misoprostol			

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Chitaishvili, D., Asatiani, T., Sublingual misoprostol prior to manual vacuum aspiration for reducing blood loss at 8-12 weeks of gestation: a randomized double-blind placebo-controlled study, Georgian medical news, 26-30, 2007 **Ref Id** 771157 **Country/ies where the study was carried out** Georgia **Study type** Randomised controlled trial **Aim of the study** To evaluate the cervical priming effect of sublingual misoprostol (compared to placebo) prior to surgical termination of pregnancy **Study dates** July 2005 - September 2006 **Source of funding**	**Sample size** n=349 randomised (n=175 misoprostol; n=174 placebo) Note. 1 women in the misoprostol arm and 2 women in the placebo arm were excluded from the study; unclear if this was before or after randomisation **Characteristics** Age in years (mean; standard deviation in parentheses): Misoprostol: 27.8 (5.4) Placebo: 27.2 (5.0) Gestational age in weeks (mean; standard deviation in parentheses): Misoprostol: 9.9 (1.4) Placebo: 9.8 (1.3) Parity (mean; standard deviation in parentheses): Misoprostol: 5.7 (4.3) Placebo: 4.9 (2.8) Previous terminations (mean; standard deviation in parentheses): Misoprostol: 3.2 (3.8) Placebo: 2.5 (2.4) **Inclusion criteria** Healthy women with a normal intrauterine pregnancy between	All women received a medical check, including haemoglobin and haematocrit screening. Women received study medication approximately 1 hour before the scheduled termination and were observed during the interval between medication and termination and asked to fill out a questionnaire regarding pre-operative side effects. The termination was performed using manual vacuum aspiration; no further details were reported. **Misoprostol:** Women received 400mcg misoprostol sublingually approximately 1 hour before the scheduled termination **Placebo:** Women received a sublingual placebo approximately 1 hour before the scheduled termination	**Outcome: Pre-operative pain (abdominal):** Misoprostol: 41/175 Placebo: 16/174 **Outcome: pre-operative bleeding:** Misoprostol: 71/175 Placebo: 0/174	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated Allocation concealment: low risk, numbered opaque sealed envelopes Blinding of participants and personnel: women were blind to treatment allocation, unclear if physicians were; low risk for objective outcomes; low risk for subjective patient-reported outcomes; unclear risk for subjective physician-reported outcomes Blinding of outcome assessment: women were blind to treatment allocation, unclear if physicians were; low risk for objective outcomes; low risk for subjective patient-reported outcomes; unclear risk for subjective physician-reported outcomes Attrition: low risk for all outcomes; all treated per protocol and no missing data Selective reporting: moderate risk, all outcomes reported in sufficient detail with the exception of satisfaction

Study details	Participants	Interventions	Outcomes and Results	Comments
No sources of funding reported	8 and 12 weeks' gestation requesting termination of pregnancy **Exclusion criteria** Contraindication to misoprostol; suspected ectopic pregnancy; spontaneous abortion; aged <18 years			**Other information** None
Full citation de Jonge, E. T., Jewkes, R., Levin, J., Rees, H., Randomised controlled trial of the efficacy of misoprostol used as a cervical ripening agent prior to termination of pregnancy in the first trimester, South African Medical Journal. Suid-Afrikaanse Tydskrif Vir GeneeskundeSamj, S, 90, 256-62, 2000 **Ref Id** 771539 **Country/ies where the study was carried out** South Africa **Study type** Randomised controlled trial **Aim of the study**	**Sample size** n=278 randomised (n=135 misoprostol; n=143 placebo) n=276 per protocol (n=135 misoprostol; n=141 placebo [n=2 withdrew from study before treatment]) n=273 included in analysis for primary outcome (n=133 misoprostol [n=2 missing primary and secondary outcome data]; n=140 placebo [n=1 missing primary and secondary outcome data]) **Characteristics** Age in years (mean; standard deviation in parentheses): Misoprostol: 27.4 (6.85) Placebo: 27.5 (6.75) Gestational age in days (mean; standard deviation in parentheses): Misoprostol: 61.9 (9.67)	All women were assessed and received counselling prior to the termination. On the day of the termination, women were given the study medication and instructed to run them under a tap for approximately 10 seconds and then insert them as high as possible into the vagina. Following a 2 to 3 hour wait, the termination was performed using manual vacuum aspiration under a paracervical block. Women were discharged 1 to 2 hours after the procedure if there were no complications. **Misoprostol:** 600mcg misoprostol (3 tablets) **Placebo:**	**Outcome: Incomplete abortion:** <u>Procedure unsuccessful</u> Misoprostol: 1/133 Placebo: 2/140 <u>Procedure impossible</u> Misoprostol: 7/133 Placebo: 16/140 **Outcome: Pre-operative pain:** Misoprostol: 83/133 Placebo: 53/140	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: unclear risk, insufficient information reported Allocation concealment: unclear risk, insufficient information reported Blinding of participants and personnel: low risk, double blind Blinding of outcome assessment: low risk, double blind Attrition: low risk for all outcomes Selective reporting: low risk, all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
To determine the efficacy, feasibility and safety of vaginal misoprostol for cervical priming prior to surgical termination of pregnancy **Study dates** July 1998 to October 1998 **Source of funding** No sources of funding reported	Placebo: 61.6 (8.52) Gravidity (mean; standard deviation in parentheses): Misoprostol: 2.82 (1.55) Placebo: 2.71 (1.65) Parity (mean; standard deviation in parentheses): Misoprostol: 1.81 (1.57) Placebo: 1.68 (1.49) Previous termination (number; percentage in parentheses): Misoprostol: 9 (7) Placebo: 10 (7) **Inclusion criteria** Women requesting a termination with a pregnancy less than 13 weeks (as confirmed by ultrasound) **Exclusion criteria** Symptomatic asthma or cardiac disease; requiring anticoagulant treatment; haemoglobin ≤8g/dl; serious comorbidities	750mg ascorbic acid (3 tablets)		
Full citation Inal, M.M., Ertopcu, K., Arici, A., Ozelmas, I., The effect of oral versus vaginal misoprostol on cervical dilatation in first-trimester abortion: a double-blind, randomized study, European Journal of	**Sample size** n=120 randomised (n=30 vaginal misoprostol; n = 30 vaginal placebo; n=30 oral misoprostol [not of interest]; n=30 oral placebo [not of interest])	All women received study medication 10 hours before the scheduled termination; the termination was performed under local anaesthesia using Carmen cannulas	**Outcome: Pre-operative bleeding** Vaginal misoprostol: 12/30 Vaginal placebo: 0/30	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: unclear risk, not reported

Study details	Participants	Interventions	Outcomes and Results	Comments
Contraception and Reproductive Health Care, 8, 197-202, 2003 **Ref Id** 159811 **Country/ies where the study was carried out** Turkey **Study type** Randomised controlled trial **Aim of the study** To determine the effectiveness of oral misoprostol and vaginal misoprostol on cervical dilation prior to first trimester surgical termination of pregnancy (not interested in oral misoprostol arm) **Study dates** Study dates not reported **Source of funding** No sources of funding reported	**Characteristics** Characteristics of women included in the study are not reported **Inclusion criteria** Inclusion criteria were not reported **Exclusion criteria** Exclusion criteria were not reported	**Vaginal misoprostol:** 200mcg misoprostol administered vaginally **Vaginal placebo:** Placebo administered vaginally (agent not reported)		Allocation concealment: unclear risk, not reported Blinding of participants and personnel: low risk, double-blind Blinding of outcome assessment: low risk, double-blind Attrition: low risk for all outcomes; no drop-out or missing data Selective reporting: low risk, all outcomes reported in sufficient detail for analysis **Other information** None
Full citation Li, C. F., Chan, C. W., Ho, P. C., A comparison of isosorbide mononitrate and misoprostol cervical ripening before suction	**Sample size** n=126 randomised (n=42 vaginal misoprostol; n =42 placebo; n=42 isosorbide mononitrate [not of interest])	All women received study medication 4 to 6 hours before scheduled termination. Study drugs were placed in the vagina by nursing staff on duty and	**Outcome: Cumulative force required for dilation (N) of cervix to 8mm:**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool

Study details	Participants	Interventions	Outcomes and Results	Comments
evacuation, Obstetrics & GynecologyObstet Gynecol, 102, 583-8, 2003 **Ref Id** 771431 **Country/ies where the study was carried out** China **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of vaginal misoprostol, isosorbide mononitrate and placebo for cervical priming prior to suction termination of pregnancy in the first trimester (not interested in isosorbide mononitrate arm) **Study dates** January 2000 to December 2001 **Source of funding** Training and Research Assistance Scheme of the Queen Mary Hospital Charity Trust	**Characteristics** Age in years (mean; standard deviation in parentheses): Vaginal misoprostol: 26 (6) Placebo: 28 (6) Gestation age in weeks (mean; standard deviation in parentheses): Vaginal misoprostol: 10 (1) Placebo: 10 (1) Gravidity (mean; standard deviation in parentheses): Vaginal misoprostol: 3 (1) Placebo: 3 (2) Parity (mean; standard deviation in parentheses): Vaginal misoprostol: 1 (1) Placebo: 1 (1) Prior termination (number; percentage in parentheses): Vaginal misoprostol: 26 (62) Placebo: 24 (57) **Inclusion criteria** Women requesting termination of pregnancy between 9 and 12 weeks' gestation in good general health; most requested termination to be done under general anaesthesia	women remained in bed until the procedure; side effects and vital signs were assessed 3 hours after the medication as administered. All terminations were performed using suction evacuation under general anaesthesia **Vaginal misoprostol:** 400mcg misoprostol inserted vaginally **Placebo:** Placebo inserted vaginally (agent not reported)	Vaginal misoprostol: N=42, M=5, SD=6 Placebo: N=42, M=12, SD=14 **Outcome: Pre-operative pain (abdominal)** <u>Mild</u> Vaginal misoprostol: 9/42 Placebo: 10/42 Moderate/severe <u>Vaginal</u> misoprostol: 18/42 Placebo: 0/42 **Outcome: Pre-operative bleeding:** <u>Mild</u> Vaginal misoprostol: 9/42 Placebo: 2/42 <u>Moderate/severe</u> Vaginal misoprostol: 8/42 Placebo: 0/42	Random sequence generation: low-risk, computer generated; stratified by parity Allocation concealment: low risk, sequentially numbered envelopes Blinding of participants and personnel: low risk, double blind Blinding of outcome assessment: low risk, double blind Attrition: low risk for all outcomes; no drop-out or missing data Selective reporting: low risk, all outcomes reported in sufficient detail **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	Exclusion criteria No additional criteria reported			
Full citation Meirik, O., My Huong, N. T., Piaggio, G., Bergel, E., von Hertzen, H., W. H. O. Research Group on Postovulatory Methods of Fertility Regulation, Complications of first-trimester abortion by vacuum aspiration after cervical preparation with and without misoprostol: a multicentre randomised trial.[Erratum appears in Lancet. 2012 Jun 23;379(9834):2342], Lancet, 379, 1817-24, 2012 **Ref Id** 771391 **Country/ies where the study was carried out** International (9 countries; not reported) **Study type** Randomised controlled trial **Aim of the study** To determine the efficacy of cervical priming with vaginal misoprostol prior to termination	**Sample size** n=6,812 assessed for eligibility (n=1,088 not eligible [n=807 unwilling to return for follow-up visit]) n=5,724 eligible (n=752 declined participation) n=4,972 randomised (n=2,485 vaginal misoprostol; n=2,487 placebo) n=4,971 included in analysis of pre-operative outcomes (n=2,484 vaginal misoprostol [n=1 reversed decision]; n=2,487 placebo) n=4,970 included in analysis of surgical outcomes (n=2,483 vaginal misoprostol [n=1 dilation failed]; n=2,487 placebo) n=4,858 included in analysis of complications (n=2,427 vaginal misoprostol [n=56 lost to follow-up; reasons not reported]; n=2,431 placebo [n=56 lost to follow-up; reasons not reported) **Characteristics** Age in years (mean; standard deviation in parentheses): Vaginal misoprostol: 26.8 (6.1) Placebo: 26.7 (6.0)	At admission, demographic, medical, gynaecological and obstetric histories were taken and haemoglobin concentration was measured; other tests were done according to centre policy. Gestational age was confirmed via ultrasound and women received study medication 3 hours before the scheduled termination; women were interviewed about side effects of the medication prior to the termination. The termination was done as an outpatient procedure, with the exception of 1 centre, but equipment varied (manual vacuum aspiration and soft aspiration tubes; electrical aspiration and soft aspiration tubes; or electrical aspiration and rigid, metal aspiration tubes), as did sedation/anaesthesia (paracervical block, general anaesthesia, no analgesia; baseline cervical dilation was measured prior to starting the procedure. All women rested for 2 to 6	**Outcome: Incomplete abortion requiring re-evacuation:** Nulliparous Vaginal misoprostol: 8/1074 Placebo: 15/1070 Parous Vaginal misoprostol: 6/1353 Placebo: 33/1361 **Outcome: Cervical trauma (tear):** Nulliparous Vaginal misoprostol: 0/1086 Placebo: 0/1086 Parous Vaginal misoprostol: 0/1397 Placebo: 2/1401 **Outcome: Uterine perforation:** Nulliparous Vaginal misoprostol: 0/1086 Placebo: 0/1086	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated permuted blocks of 8, 10 and 12 stratified by centre and developed by coordinating centre (HRP/WHO) Allocation concealment: low risk, sequentially numbered sealed envelopes Blinding of participants and personnel: low risk, double blind Blinding of outcome assessment: low risk, women and physician blind to treatment allocation, unclear if clinic staff were at follow-up but outcomes were objective Attrition: low risk for all outcomes: loss to follow-up low (~2%) and equivalent across groups but reasons are not reported Selective reporting: low risk, all outcomes reported in sufficient detail for analysis **Other information**

Study details	Participants	Interventions	Outcomes and Results	Comments
of pregnancy with vacuum aspiration **Study dates** October 2002 to September 2005 **Source of funding** UN Development Programme/UN Population Fund/WHO/World Bank Special Programme of Research; Development and Research Training in Human Reproduction, Department of Reproductive Health and Research, WHO; Packard Foundation	Gestational age in weeks (mean; standard deviation in parentheses): Vaginal misoprostol: 7.9 (2) Placebo: 7.9 (2) Nulliparous (number; percentage in parentheses): Vaginal misoprostol: 1,087 (44) Placebo: 1,086 (44) Previous surgical termination (number percentage in parentheses): Vaginal misoprostol: 944 (38) Placebo: 926 (37) **Inclusion criteria** Women with a single intrauterine pregnancy with gestational age of 11^{+1} weeks or less (originally 12 weeks but amended due to misunderstanding across centres) on the day of the termination; willing to attend follow-up; able to give informed consent and understand procedures **Exclusion criteria** Medical conditions requiring alteration to study procedure; contraindications to misoprostol or prostaglandin analogues;	hours following the termination before discharge unless they were admitted on the day of the termination (some women were sterilised at the same time and were admitted). Women were contacted at 7 to 14 days follow-up to records complications. **Vaginal misoprostol:** Two 200mcg misoprostol tablets were administered vaginally 3 hours prior to scheduled termination **Placebo:** Two placebo tablets (agent not specified) were administered vaginally 3 hours prior to scheduled termination	<u>Parous</u> Vaginal misoprostol: 3/1397 Placebo: 1/1401 **Outcome: Pre-operative pain (abdominal):** Vaginal misoprostol: 1355/2484 Placebo: 545/2487 **Outcome: Pre-operative bleeding:** Vaginal misoprostol: 909/2484 Placebo: 167/2487	None

Study details	Participants	Interventions	Outcomes and Results	Comments
	haemoglobin ≤100g/L (one centre did not admit nulliparous women or those with a previous caesarean section			
Full citation Saav, I., Kopp Kallner, H., Fiala, C., Gemzell-Danielsson, K., Sublingual versus vaginal misoprostol for cervical dilatation 1 or 3 h prior to surgical abortion: a double-blinded RCT, Human Reproduction, 30, 1314-22, 2015 **Ref Id** 771178 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** "The primary objective was to compare, in a placebo controlled double-blind RCT, the baseline cervical dilatation after sublingual administration of misoprostol with the well-established vaginal administration of misoprostol,	**Sample size** N = 184 were randomised of whom N = 178 were included in the analyses (N = 6 were excluded due to 'priming interval being outside the defined limits' [N = 4] and 'not meeting inclusion criteria' [N = 2]) **Characteristics** Sublingual priming 1 hour (SL 1h): N = 45; mean (range) gestational age = 64.5 (47-84) days; mean (range) BMI = 22.9 (17.2-33.2) kg/m2; mean (range) age = 22.9 (18-34) years; mean (range) priming time = 64.5 (56-77) mins. Sublingual priming 3 hours (SL 3h): N = 46; mean (range) gestational age = 63 (43-84) days; mean (range) BMI = 22.5 (17.8-28.6) kg/m2; mean (range) age = 23.6 (18-34) years; mean (range) priming time = 180 (120-210) mins. Vaginal priming 1 hour (PV 1h): N = 43; mean (range) gestational age = 64.8 (42-84) days; mean (range) BMI = 22 (17.4-31.6) kg/m2; mean	Random allocation to cervical dilation according to 1 of the following procedures: - SL 1h: 400mcg sublingual misoprostol 1 hour before vacuum aspiration + vaginal placebo - SL 3 h:400mcg sublingual misoprostol 3 hours before vacuum aspiration + vaginal placebo - PV 1 h: 400mcg vaginal misoprostol 1 hour before vacuum aspiration + sublingual placebo - PV 3 h: 400mcg vaginal misoprostol 3 hours before vacuum aspiration + sublingual placebo The tablets were self-administered by the women, who also received 100mg oral diclofenac at the time of misoprostol. Study protocol violations occurred if priming time < 50 min or > 90 min in the 1-hour groups and < 2 hours or > 3.5 hours in the 3-hour groups. "The vacuum aspiration was performed	**Outcome: Cervical trauma:** SL 1h: 0/45 SL 3h: 0/46 PV 1h: 0/43 PV 3h: 0/44 **Outcome: Uterine perforation:** SL 1h: 0/45 SL 3h: 0/46 PV 1h: 0/43 PV 3h: 0/44 **Outcome: Force required to dilate cervix** Peak N SL 1h: M=16.5, SD=8, N=45 SL 3h: M=17.1, SD=8.4, N=46 PV 1h: M= 20.3, SD=10.6, N=43 PV 3h: M=15.5, SD=8.2, N=44 Cumulative N to dilate up to 9.7mm	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; computer-generated list; the person responsible for generating the randomisation list did not take part in enrolment Allocation concealment: Low risk; sequentially numbered opaque sealed envelopes; the person responsible for sealing the envelopes did not take part in enrolment Blinding of participants and personnel: Women and personnel blinded for route of administration, but not for priming interval; low risk for all reported outcomes as they are also somewhat objective outcomes apart from pre-operative pain, which is at high risk of performance bias. Blinding of outcome assessment: Women and personnel blinded for route of administration, but not for priming interval; low risk for all reported outcomes as they are

Study details	Participants	Interventions	Outcomes and Results	Comments
when administered at 1 h prior to surgical termination of pregnancy. Secondary objectives included a comparison of the efficacy of misoprostol administered by the sublingual or vaginal routes at a 1 or 3 h interval in baseline dilatation and cumulative force used for mechanical dilation, and to evaluate the side effects, blood loss and acceptability by the women undergoing treatment." (p. 1315) **Study dates** June 2007 - March 2014 **Source of funding** The Swedish research council (521-2009-2605), Swedish Council for Working Life and Social Research (1404/08), Stockholm County Council and Karolinska Institutet (ALF 2009-2012)	(range) age = 23.2 (18-37) years; mean (range) priming time = 64.1 (54-78) mins. Vaginal priming 3 hours (PV 3h): N = 44; mean (range) gestational age = 66 (47-85) days; mean (range) BMI = 21.7 (15.8-28.3) kg/m2; mean (range) age = 24.5 (18-37) years; mean (range) priming time = 185 (127-187) mins. There were no significant differences in gestational age, BMI or age between the groups. **Inclusion criteria** Women who were aged > 18 years, willing and able to participate and give informed consent, of good health, nulliparous, and requesting surgical termination of a pregnancy with a gestational age of 6 to 13 weeks. Previous pregnancy was not an exclusion criterion, but the pregnancies of the participating women who had been pregnant previously had either resulted in miscarriage or termination in the first trimester **Exclusion criteria** Women with (1) any contraindication to misoprostol,	under general anaesthesia according to clinical routine, which allows the women to choose between local and general anaesthesia. Dilatation was performed using tapered Pratt-dilatators" (p. 1316).	SL 1h: M=51.9, SD=27, N=45 SL 3h: M=54.4, SD=29.2, N=46 PV 1h: M=64.6, SD=31.3, N=43 PV 3h: M=47.1, SD=23.3, N=44 **Outcome: Pre-operative pain (abdominal):** SL 1h: 30/45 SL 3h: 31/46 PV 1h: 6/43 PV 3h: 24/44 **Outcome: Pre-operative expulsion of fetus (complete expulsion):** SL 1h: 0/45 SL 3h: 0/46 PV 1h: 0/43 PV 3h: 0/44 **Outcome: Pre-operative bleeding:** SL 1h: 2/45 SL 3h: 15/46	also somewhat objective outcomes apart from pre-operative pain, which is at high risk of detection bias. Attrition: Low risk; ITT analyses done for all outcomes; data included for 178/184 randomised women. Selective reporting: Low risk Other bias: None reported **Other information** Non-inferiority study testing if SL 1h is non-inferior to SL 3h for baseline ditation, peak force and cumulative force.

Study details	Participants	Interventions	Outcomes and Results	Comments
	(2) untreated genital infection, (3) previous history of surgery to the cervix, or (4) abnormal pregnancy.		PV 1h: 3/43 PV 3h: 8/44	
Full citation Saxena, P., Salhan, S., Sarda, N., Role of sublingual misoprostol for cervical ripening prior to vacuum aspiration in first trimester interruption of pregnancy, Contraception, 67, 213-217, 2003 **Ref Id** 771080 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study** To evaluate the effectiveness of sublingual misoprostol for cervical priming prior to vacuum aspiration **Study dates** Study dates not reported	**Sample size** n=50 randomised (n=50 sublingual misoprostol; n=50 Control) Characteristics Age in years (mean; standard deviation in parentheses): Sublingual misoprostol: 26.3 (8.5) Control: 25.2 (6.8) Gestation age in weeks (mean) Sublingual misoprostol: 7.7 Control: 7.9 Parity (mean; standard deviation in parentheses): Sublingual misoprostol: 3.1 (2.1) Control: 3.4 (2.0) Previous termination (number; percentage in parentheses): Sublingual misoprostol: 18 (36) Control: 16 (32) **Inclusion criteria** Women with a gestational age between 6 and 12 weeks (confirmed by menstrual history and pelvic examination; ultrasound if discrepancy	All women had a history taken, a physical and pelvic examination, and investigations of haemoglobin, urine, blood group and Rhesus type. Side effects of cervical priming were assessed pre-operatively and baseline cervical dilation was assessed prior to starting the termination; women with insufficient dilation were given a paracervical block to facilitate further dilation. The termination was completed using suction evacuation with Karman's cannula, followed by check curettage. All women were given 2 days of analgesics and 5 days of antibiotics at discharge and were followed up at 7 to 10 days and 1 month (or the first menstrual period). **Sublingual misoprostol:** 400mcg misoprostol given sublingually 3 hours prior to the scheduled termination	**Outcome: Incomplete abortion:** Vaginal misoprostol: 0/50 Control: 0/50 **Outcome: Cervical trauma (laceration):** Vaginal misoprostol: 0/50 Control: 1/50 **Outcome: Uterine perforation:** Vaginal misoprostol: 0/50 Control: 1/50	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: unclear risk, not reported Allocation concealment: unclear risk, not reported Blinding of participant and personnel: no blinding of women, unclear if physicians were blinded; low risk for objective outcomes; high risk for subjective outcomes Blinding of outcome assessment: no blinding of women, unclear if physicians were blinded; low risk for objective outcomes; high risk for subjective outcomes Attrition: low risk for all outcomes; no drop-out or loss to follow-up Selective reporting: low risk, all outcomes reported in sufficient detail for analysis **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding Central Scientific and Industrial Research Organization	between the two); good general health **Exclusion criteria** Previous uterine surgery; contraindications to prostaglandins; current infection; haemoglobin <9gm%; current IUD; uterine anomaly; chronic maternal illness	**Control:** No cervical priming agent given		
Full citation Saxena, P., Salhan, S., Sarda, N., Sublingual versus vaginal route of misoprostol for cervical ripening prior to surgical termination of first trimester abortions, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 125, 109-13, 2006 **Ref Id** 771139 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study**	**Sample size** n=118 assessed for eligibility (n=6 hypertension; n=7 uterine scar; n=3 gestational age >12 weeks; n=1 asthma; n=1 declined to participate) n=100 randomised (n=50 sublingual misoprostol; n=50 vaginal misoprostol) **Characteristics** Age in years (mean; standard deviation in parentheses): Sublingual misoprostol: 27.3 (3.5) Vaginal misoprostol: 26.8 (3.4) Gestational age in weeks (mean; standard deviation in parentheses): Sublingual misoprostol: 8.1 (0.9) Vaginal misoprostol: 8.0 (1.1) Parity (mean; standard deviation in parentheses):	All women had a history taken, a physical and pelvic examination, and investigations of haemoglobin, urine, blood group and Rhesus type. Side effects, blood pressure, pulse, and temperature were measured pre-operatively and baseline cervical dilation was measured prior to the termination; women with insufficient dilation were given a paracervical block to facilitate further dilation. Suction evacuation was performed using Karmans cannulas and then the uterus was curetted gently. Women were discharged after 3 to 4 hours were given 2 days of analgesics and 5 days of antibiotics. All women were followed up at 7 to 10	**Outcome: Pre-operative pain:** Sublingual misoprostol: 12/50 Vaginal misoprostol: 7/50 **Outcome: Pre-operative expulsion of the fetus** Sublingual misoprostol: 0/50 Vaginal misoprostol: 0/50 **Outcome: Pre-operative bleeding:** Sublingual misoprostol: 22/50 Vaginal misoprostol: 11/50	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: high risk, sequentially allocated, not true randomisation Allocation concealment: high risk, no concealment Blinding of participant and personnel; no blinding of personnel or investigators administering medication; physician performing termination was blind to treatment allocation; unclear if investigators collecting side effect and follow-up data were aware of treatment allocation; low risk for objective outcomes; high risk for patient-reported subjective outcomes; low risk for physician (conducting termination) reported outcomes

Study details	Participants	Interventions	Outcomes and Results	Comments
To compare the efficacy and acceptability of sublingual and vaginal misoprostol for cervical priming prior to vacuum aspiration for termination of pregnancy **Study dates** January 2002 to June 2002 **Source of funding** No sources of funding reported	Sublingual misoprostol: 3.1 (2) Vaginal misoprostol: 3.6 (2.0) Previous termination (number; percentage in parentheses): Sublingual misoprostol: 21 (42) Vaginal misoprostol: 19 (38) **Inclusion criteria** Women requesting a termination, who were in general good health, with a pregnancy between 6 and 12 weeks **Exclusion criteria** Previous uterine surgery; contraindications to prostaglandins; haemoglobin <9g%; current IUD; uterine anomalies; current infection; chronic disease that may affect drug metabolism	days and 1 month (or the first menstrual period). **Sublingual misoprostol:** Women were told to take 400mcg misoprostol sublingually at 7.30am on the day of the scheduled termination. They were asked to arrive at the hospital by 9.30am and to record any side effects from the misoprostol and how long it took the misoprostol to dissolve. **Vaginal misoprostol:** Women were told to arrive at the hospital by 7.30 am on the day of the scheduled termination. 400mcg misoprostol was inserted into the posterior fornix of the vagina (after wetting the tablet with water) by the recruiting investigator.		Blinding of outcome assessment: no blinding of personnel or investigators administering medication; physician performing termination was blind to treatment allocation; unclear if investigators collecting side effect and follow-up data were aware of treatment allocation; low risk for objective outcomes; high risk for patient-reported subjective outcomes; low risk for physician (conducting termination) reported outcomes Attrition: low risk for all outcomes; no drop-out or loss to follow-up Selective reporting: low risk, all outcomes reported in sufficient detail **Other information** None
Full citation Saxena, P., Sarda, N., Salhan, S., Nandan, D., A randomised comparison between sublingual, oral and vaginal route of misoprostol for pre-abortion cervical ripening in first-trimester pregnancy termination under	**Sample size** n=228 assessed for eligibility (n=16 hypertension; n=5 uterine scar; n=4 gestational age >12 weeks; n=2 declined participation; n=1 heart disease) n=200 randomised (n=50 sublingual misoprostol; n=50	All women had a history taken, a physical and pelvic examination, and investigations of haemoglobin, urine, blood group and Rhesus type; side effects were recorded pre-operatively. All women received IV analgesia	**Outcome: Pre-operative pain:** Sublingual misoprostol: 21/50 Vaginal misoprostol: 17/50	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated

Study details	Participants	Interventions	Outcomes and Results	Comments
local anaesthesia, Australian & New Zealand journal of obstetrics & gynaecology, 48, 101-6, 2008 **Ref Id** 770944 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy or sublingual, oral and vaginal misoprostol for cervical priming prior to suction evacuation for termination (oral misoprostol not of interest) **Study dates** Study dates not reported **Source of funding** No sources of funding reported	vaginal misoprostol; n=50 oral misoprostol [not of interest]; n=50 control) **Characteristics** Age in years (mean; standard deviation reported in parentheses): Sublingual misoprostol: 26.6 (2.2) Vaginal misoprostol: 26.8 (3.4) Control: 27.4 (2.8) Gestational age in weeks (mean): Sublingual misoprostol: 7.9 Vaginal misoprostol: 8.0 Control: 7.6 Parity (mean; standard deviation in parentheses): Sublingual misoprostol: 3.5 (2) Vaginal misoprostol: 3.5 (2) Control: 3.8 (2) Previous termination (number; percentage in parentheses): Sublingual misoprostol: 20 (40) Vaginal misoprostol: 16 (32) Control: 18 (32) **Inclusion criteria** Healthy women requesting a termination of pregnancy with a gestation between 6 and 12	(pentazocine 30 mg + diazepam 10 mg) and baseline cervical dilation was assessed; women with insufficient dilation were given a paracervical block to facilitate further dilation. The termination was performed using suction with a cannula appropriate for the size of the gestation period; this was followed by check curettage. Women were given 2 days of analgesics and 5 days of antibiotics and told to return if bleeding persisted for more than 3 days or if they developed fever or pain in lower abdomen. All women were followed up at 7 to 10 days and 1 month (or the first menstrual period). **Sublingual misoprostol:** Women were told to take 400mcg sublingually at 7am on the day of the scheduled termination. They were asked to arrive at the hospital by 9.00am and to record any side effects from the misoprostol and how long it took the misoprostol to dissolve	**Outcome: Pre-operative expulsion of the fetus** Sublingual misoprostol: 0/50 Vaginal misoprostol: 0/50 **Outcome: Pre-operative bleeding:** Sublingual misoprostol: 26/50 Vaginal misoprostol: 17/50	Allocation concealment: unclear risk, insufficient information reported; list was placed in a sealed envelope - investigators may have been able to see whole list and therefore know which treatment allocation the next woman would receive Blinding of participant and personnel; no blinding of personnel or investigators administering medication; physician performing termination was blind to treatment allocation; unclear if investigators collecting side effect and follow-up data were aware of treatment allocation; low risk for objective outcomes; high risk for patient-reported subjective outcomes; low risk for physician (conducting termination) reported outcomes Blinding of outcome assessment: no blinding of personnel or investigators administering medication; physician performing termination was blind to treatment allocation; unclear if investigators collecting side effect and follow-up data were aware of treatment allocation; low risk for objective outcomes; high risk for patient-reported subjective outcomes; low risk for physician (conducting termination) reported outcomes

Study details	Participants	Interventions	Outcomes and Results	Comments
	weeks (estimated and confirmed by ultrasound if any doubt) **Exclusion criteria** Previous uterine surgery; contraindication to misoprostol; current IUD; current infection; on long term medication (not specified what for); uterine abnormality	**Vaginal misoprostol:** Women were told to arrive at the hospital by 7.00 am on the day of the scheduled termination. 400mcg misoprostol was inserted into the posterior fornix of the vagina (after wetting the tablet with water) by the recruiting investigator. **Control:** No cervical priming agent given		Attrition: low risk for all outcomes; no drop-out or loss to follow-up Selective reporting: low risk, all outcomes reported in sufficient detail **Other information** None
Full citation Sharma, S., Refaey, H., Stafford, M., Purkayastha, S., Parry, M., Axby, H., Oral versus vaginal misoprostol administered one hour before surgical termination of pregnancy: a randomised controlled trial, 112, 456-60, 2005 **Ref Id** 770964 **Country/ies where the study was carried out** United Kingdom **Study type**	**Sample size** N = 90 **Characteristics** Oral priming 1 hour (O 1h): N = 30; mean (SD) age = 27.5 (5) years; median gestational age = 9.21 weeks; primiparous 53%; median priming time = 70 mins [not of interest] Vaginal priming 1 hour (PV 1h): N = 30; mean (SD) age = 25.5 (5.5) years; median gestational age = 9.21 weeks; primiparous 73%; median priming time = 75 mins. Standard care (con): N = 30; mean (SD) age = 24.5 (5.9) years; median gestational age = 8.64 weeks; primiparous 77%;	Random allocation to 1 of the following procedures: - O 1h: 400mcg oral misoprostol 1 hour before surgical termination done with Karman suction curette under general anaesthesia [not of interest] - PV 1h: 800mcg vaginal misoprostol 1 hour before surgical termination done with Karman suction curette under general anaesthesia - Con: Standard care involving no cervical priming before surgical termination done with Karman suction	**Outcome: Cervical trauma:** Not directly reported, but study reports "All women in the study had an uncomplicated procedure." (p. 458) PV: 1h 0/30 Con 0/30 **Outcome: Uterine perforation:** Not directly reported, but study reports "All women in the study had an uncomplicated	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; computer-generated list; the person responsible for generating the randomisation list did not take part in enrolment Allocation concealment: Unclear risk; no information reported Blinding of participants and personnel: Unblinded, but probably low risk for the reported outcomes apart from pain and bleeding, which are at high risk. Blinding of outcome assessment: Unblinded, but

Study details	Participants	Interventions	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** "To assess the efficacy of oral and vaginal misoprostol as cervical priming agents administered 1 hour before first trimester surgical termination of pregnancy." (p 456) **Study dates** September 2001 - September 2002 **Source of funding** Hospital League of Friends, Chelsea and Westminster Hospital	median priming time = not applicable. "Despite randomisation, the oral misoprostol group seems to have a lower percentage of primiparous women." (p. 457) The authors have therefore also included some results that are adjusted for parity. **Inclusion criteria** Healthy women aged ≥ 18 years, requesting a surgical termination of an ultrasound-confirmed intrauterine pregnancy of 7 to 10 weeks' gestation, able to give informed consent and no contraindication to the use of misoprostol (e.g. known intolerance or history of cardiac disease). **Exclusion criteria** Pregnant women with symptoms or signs of threatened miscarriage	curette under general anaesthesia	procedure." (p. 458) PV 1h: 0/30 Con: 0/30 **Outcome: Cumulative force required to dilate cervix (N)** PV 1h: M=50.6, 95% CI=23.1-111), N=29 Con: M=70.1, 95% CI=40.2-122.3, N=30 **Outcome: Pre-operative pain (abdominal pain necessitating analgesia)** PV 1h: 1/30 Con: 0/30 **Outcome: Pre-operative bleeding ("moderate amount of blood" p. 458):** PV 1h: 0/30 Con: 0/30	probably low risk for the reported outcomes apart from pain and bleeding, which are at high risk. Attrition: Unclear risk; no flow data reported so unclear if any women lost at the different stages of the study. Selective reporting: Probably low risk Other bias: None reported **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Sharma, M., Sublingual misoprostol for cervical priming in surgical first trimester pregnancy termination, Journal of Obstetrics & Gynaecology of IndiaJ Obstet Gynaecol India, 61, 531-3, 2011 **Ref Id** 771308 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study** "To determine the efficacy of 400 mcg sublingual misoprost as an adjunct to suction evacuation in first trimester pregnancy termination." (p. 531) **Study dates** January 2006 – June 2007 **Source of funding** Not reported	**Sample size** N = 221 **Characteristics** Sublingual priming 3 hours (SL 3h): N = 121; mean (?, SD?) gestational age = 7.06 (1.4) weeks; mean (? SD?) parity = 1.66 (0.99); mean (SD?) age = 24.77 (7.18) years. Control (con): N = 100; mean (?, SD?) gestational age = 7 (1.7) weeks; mean (? SD?) parity = 1.78 (1.4); mean (SD?) age = 24.69 (4.17) years. None of these baseline characteristics differed significantly between the groups. **Inclusion criteria** Women with gravidity ≤4 and a gestational age between 5 to 12 weeks. **Exclusion criteria** Women with gravidity >4, gestational age >12 weeks, cardiorespiratory disorders, or haemoglobin <8.0 g/dl.	Random allocation to cervical priming or control (no cervical priming): - SL 3h: 400mcg sublingual misoprostol 3 hours before suction evacuation - Con: Control group receiving no cervical priming prior to dilatation and suction evacuation	**Outcome: Incomplete abortion (need for re-evacuation or re-aspiration)** SL 3h: 4/121 Con: 2/100 **Outcome: Uterine perforation:** SL 3h: 6/121 Con: 4/100 **Outcome: Pre-operative pain:** SL 3h: 9/121 Con: 20/100 Please note, this outcome is reported as "No. of women having abdominal pain". It is therefore not clear whether this is pre-operative pain or not. **Outcome: Pre-operative bleeding:** SL 3h: 9/121 Con: 2/100 Please note, this outcome is reported	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Unclear risk; study described as randomised in the abstract, but no further information reported. Allocation concealment: Unclear risk; study described as randomised in the abstract, but no further information reported. Blinding of participants and personnel: Unclear risk, no information reported. Blinding of outcome assessment: Unclear risk, no information reported. Attrition: Unclear risk; although all 221 reported women are included in the analyses, no flow details are reported, so unclear whether any women have been excluded at any stage of the study. Selective reporting: Unclear risk, the trial reports minimal methodological detail Other bias: None reported **Other information**

Study details	Participants	Interventions	Outcomes and Results	Comments
			as "Vaginal bleeding". It is therefore not clear whether this is pre-operative bleeding or not.	The trial reports minimal methodological detail and reports only in the abstract that the women were randomised. It is therefore not completely clear whether this is a genuine RCT that should be included.
Full citation Tang, O. S., Mok, K. H., Ho, P. C., A randomized study comparing the use of sublingual to vaginal misoprostol for pre-operative cervical priming prior to surgical termination of pregnancy in the first trimester, Human Reproduction, 19, 1101-4, 2004 **Ref Id** 771182 **Country/ies where the study was carried out** Hong Kong/China **Study type** Randomised controlled trial **Aim of the study** "This study aimed to compare a new route of sublingual administration to the vaginal route of administration for pre-operative cervical priming in first trimester surgical abortion." (p. 1101)	**Sample size** N = 80 **Characteristics** Sublingual priming 3 hours (SL 3h): N = 40; mean (SD) gestational age = 10.5 (1) weeks; mean (SD) weight = 53.3 (9.1) kg; mean (SD) age = 24.2 (5.8) years; % with a history of surgical termination = 27.5. Vaginal priming 3 hours (PV 3h): N = 40; mean (SD) gestational age = 10 (1.3) weeks; mean (SD) weight = 50.5 (7.3) kg; mean (SD) age = 23.3 (5.7) years; % with a history of surgical termination = 37.5. There were no significant differences in gestational age, weight, age or history of surgical termination between the groups. **Inclusion criteria**	Random allocation to cervical dilation according to 1 of the following procedures: - SL 3h: 400mcg sublingual misoprostol 3 hours before vacuum aspiration by a Karman curette under conscious sedation - PV 3h: 400mcg vaginal misoprostol 3 hours before vacuum aspiration by a Karman curette under conscious sedation 25mg fentanyl and 2 mg midazolam were given intravenously to the women before the operation.	**Outcome: Cumulative force required to dilate cervix to 8mm:** SL 3h: M=9, SD=9.8 PV 3h: M=6.6, SD=5.4 **Outcome: Pre-operative pain:** <u>Any</u>: SL 3h: 34/40 PV 3h: 31/40 <u>Mild</u>: SL 3h: 22/40 PV 3h: 17/40 <u>Moderate</u>: SL 3h: 11/40 PV 3h: 9/40 <u>Severe</u>: SL 3h: 1/40 PV 3h: 5/40	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; computer-generated list. Allocation concealment: Unclear risk; no information reported Blinding of participants and personnel: Surgeon, but not women blinded to route of administration; low risk for force and expulsion of fetus (objective outcomes), high risk for pain and bleeding (subjective outcomes). Blinding of outcome assessment: Surgeon, but not women blinded to route of administration; unclear who assessed the outcomes; low risk for force and expulsion of fetus (objective outcomes), high risk for pain and bleeding (subjective outcomes).

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates September 2001 - September 2002 **Source of funding** The Committee on Research; The University of Hong Kong of the Hong Kong Special Administrative Region, China.	Women requesting a termination of pregnancy, who were nulliparous, had a gestational age up to 12 weeks and a normal general and gynaecological history and physical examination **Exclusion criteria** Long-term medication, an intrauterine contraceptive device, heavy smoking or allergy to misoprostol		**Outcome: Pre-operative expulsion of fetus:** SL 3h: 0/40 PV 3h: 0/40 **Outcome: Pre-operative bleeding:** Any: SL 3h: 15/40 PV 3h: 9/40 Scanty: SL 3h: 12/40 PV 3h: 7/40 Moderate: SL 3h: 3/40 PV 3h: 1/40 Heavy: SL 3h: 0/40 PV 3h: 1/40	Attrition: Low risk; data included for all randomised women for all outcomes. Selective reporting: Low risk Other bias: None reported **Other information** None
Full citation Vimala, N., Mittal, S., Kumar, S., Sublingual misoprostol for preabortion cervical ripening in first-trimester pregnancy termination, Contraception, 67, 295-297, 2003 **Ref Id** 771088	**Sample size** N = 60 **Characteristics** Sublingual priming 2 hours (SL 2h): N = 30; mean (SD) gestational age = 7.8 (1.2) week; mean (SD) parity = 2.4 (1.2); mean (SD) age = 27.6	Random allocation to 1 of the following groups: SL 2h: 400mcg sublingual misoprostol 2 hours before vacuum aspiration con: 100mg sublingual pyridoxine placebo 2 hours before vacuum aspiration Analgesia consisting of an intramuscular injection of	**Outcome: Incomplete abortion (need for re-evacuation or re-aspiration):** SL 2h: 0/30; Con: 0/30 **Outcome: Uterine perforation:**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; random number table Allocation concealment: Unclear risk; sequentially numbered

Study details	Participants	Interventions	Outcomes and Results	Comments
Country/ies where the study was carried out India **Study type** Randomised controlled trial **Aim of the study** "to determine the efficacy of sublingual misoprostol in facilitating cervical dilatation before surgical abortion in first trimester pregnancy." (p. 295) **Study dates** May-June 2002 **Source of funding** Not reported	(3.8) years; prior terminations = 13.3%. Placebo (con): N = 30; mean (SD) gestational age = 7.7 (1.4) week; mean (SD) parity = 2.3 (1.5); mean (SD) age = 27.9 (4) years; prior terminations = 36.7%. The groups did not differ significantly on any of these characteristics **Inclusion criteria** Healthy women requesting a surgical termination by vacuum aspiration for a pregnancy of 6 to 11 weeks' gestation **Exclusion criteria** Medical or obstetric complication, allergy to misoprostol	75mg diclophenac sodium was available if the women experienced pain. The vacuum aspirations were performed under intravenous analgesia consisting of 10mg diazepam and 30mg pentazocin using a Karman's suction cannula (8mm diameter).	SL 2h: 0/30 Con: 0/30 **Outcome: Pre-operative pain:** SL 2h: 17/30 Con: 0/30 **Outcome: Pre-operative bleeding:** SL 2h: 21/30 Con: 4/30	opaque sealed envelopes; unclear who was responsible for preparing the envelopes Blinding of participants and personnel: Unclear risk, no information reported Blinding of outcome assessment: Unclear risk, no information reported Attrition: Unclear risk; no flow diagram included to assess drop-out at the different stages of the study Selective reporting: Probably low risk Other bias: None reported **Other information** None
Full citation Vimala, N., Mittal, S., Kumar, S., Dadhwal, V., Sharma, Y., A randomized comparison of sublingual and vaginal misoprostol for cervical priming before suction termination of first-trimester pregnancy, Contraception, 70, 117-120, 2004a	**Sample size** N = 100 **Characteristics** Sublingual priming 2 hours (SL 2h): N = 50; mean (SD) gestational age = 7.5 (2) weeks; mean (? range) body surface area = 1.4 (1.3-1.9); mean (SD) age = 28.8 (6.1) years; mean (SD) parity = 3.1 (1.8); mean	Random allocation to cervical dilation according to 1 of the following procedures: SL 2h: 400mcg sublingual misoprostol 2 hours before vacuum aspiration using a Karmans suction cannula 6 to 10 mm in diameter PV 2h: 400mcg vaginal misoprostol 2 hours	**Outcome: Incomplete abortion (need for re-evacuation or re-aspiration):** SL 2h: 0/50 PV 2h: 0/50 **Outcome: Uterine perforation:**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk; random numbers list Allocation concealment: Unclear risk; sequentially numbered

Study details	Participants	Interventions	Outcomes and Results	Comments
Ref Id 159084 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study** To compare "the efficacy and side effects of sublingual and vaginal misoprostol for cervical priming before first-trimester pregnancy termination." (p. 117) **Study dates** July to September 2002 **Source of funding** Not reported	(range) previous induced terminations = 0 (0-1); mean (? range) priming time = 132.5 (120-160) mins. Vaginal priming 2 hours (PV 2h): N = 50; mean (SD) gestational age = 7.8 (1.6) weeks; mean (? range) body surface area = 1.6 (1.4-2.6); mean (SD) age = 28.3 (4.1) years; mean (SD) parity = 3.4 (1.6); mean (range) previous induced terminations = 1 (0-3); mean (? range) priming time = 128 (120-160) mins. The groups did not differ significantly on any of these characteristics. **Inclusion criteria** Women requesting termination of a 6 to 12 week old pregnancy by vacuum aspiration **Exclusion criteria** Known allergy to misoprostol, current medical disorders, history of previous cervical surgery or caesarean section	before vacuum aspiration using a Karmans suction cannula 6 to 10 mm in diameter All the women received vacuum aspiration under intravenous analgesia consisting of 30mg pentazocin and 10mg diazepam.	SL 2h: 0/50 PV 2h: 0/50 **Outcome: Pre-operative pain:** SL 2h: 43/50 PV 2h: 41/50 **Outcome: Pre-operative bleeding:** SL 2h: 34/50; PV 2h: 18/50	opaque sealed envelopes, not clear who they were prepared by, lead investigator seems to have been involved in all aspects of the trial Blinding of participants and personnel: Unblinded; low risk for all reported outcomes apart from bleeding and pain (patient reported) which are at high risk Blinding of outcome assessment: Unblinded; low risk for all reported outcomes apart from bleeding and pain (patient reported) which are at high risk Attrition: Unclear risk; no flow diagram reported to assess the level of drop-out at the different stages of the study Selective reporting: Probably low risk Other bias: None reported **Other information** None
Full citation Vimala, N., Mittal, S., Kumar, S., Sublingual misoprostol before first trimester abortion: a comparative study using two	**Sample size** N = 120 **Characteristics**	2 random allocation schedules: (1) to 400 or 200 mcg misoprostol, (2) to cervical dilation for 2 or 3 hours:	**Outcome: Incomplete abortion (need for re-evacuation or re-aspiration):**	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool

Study details	Participants	Interventions	Outcomes and Results	Comments
dose regimens, Indian Journal of Medical Sciences, 58, 54-61, 2004b **Ref Id** 388509 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study** "To determine the optimal dosage and dosing interval for the use of misoprostol administered sublingually for pre-abortion cervical dilatation." (p. 54) **Study dates** October 2002 – January 2003 **Source of funding** Not reported	Only reported for different dose groups: Sublingual priming 400 mcg (SL400): N = 60; mean (SD) gestational age = 8.6 (1.2) weeks; mean (SD) parity = 1.2 (0.6); mean (SD) age = 22.4 (6.1) years; primigravidae = 6.6%; previous terminations = 11.8% Sublingual priming 200 mcg (SL200): N = 60; mean (SD) gestational age = 8.8 (1.6) weeks; mean (SD) parity = 1.4 (0.2); mean (SD) age = 22.8 (2.1) years; primigravidae = 8.3%; previous terminations = 14% "The two treatment groups were similar in relation to maternal age, parity and gestational age (Table 1)." (p. 57) **Inclusion criteria** Women requesting a termination of pregnancy between 6 to 11 weeks' gestation **Exclusion criteria** Heart disease, asthma, known allergy to prostaglandins,	- SL400 2h: 400mcg sublingual misoprostol 2 hours before vacuum aspiration - SL400 3h: 400mcg sublingual misoprostol 3 hours before vacuum aspiration - SL200 2h: 200mcg sublingual misoprostol 2 hours before vacuum aspiration - SL200 3h:200mcg sublingual misoprostol 3 hours before vacuum aspiration In all the groups, vacuum aspiration was performed under intravenous analgesia consisting of 30mg pentazocin and 10mg diazepam	SL400 2h 0/30 SL400 3h: 0/30 SL200: 0/60 **Outcome: Uterine perforation:** SL400 2h: 0/30 SL400 3h: 0/30 SL200: 0/60 **Outcome: Pre-operative pain requiring analgesics:** SL400 2h: 17/30 SL400 3h: 20/30 SL200: 28/60 **Outcome: Pre-operative expulsion of fetus:** SL400 2h: 0/30 SL400 3h: 0/30 SL200: 0/60 **Outcome: Pre-operative bleeding:** SL400 2h: 20/30 SL400 3h: 23/30 SL200: 36/60	Random sequence generation: Low risk; random number tables Allocation concealment: Probably low risk; sequentially numbered sealed envelopes Blinding of participants and personnel: Surgeon, but not women blinded for dose and priming interval; high risk for pain and bleeding (patient reported), low risk for the other reported outcomes Blinding of outcome assessment: Assessor, but not women blinded for dose and priming interval; high risk for pain and bleeding (patient reported), low risk for the other reported outcomes Attrition: Unclear risk; no flow diagram shown so unclear whether there was drop out at different stages of the study Selective reporting: Probably low risk Other bias: None reported **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	multiple pregnancies, and scarred uterus			

CI: confidence interval; Con: control; HRP: Human Reproduction; IUD: intrauterine device; mcg: micrograms; O: oral; PV: vaginally; RCT randomised controlled trial; SL: sublingually; UN: United Nations; WHO: World Health Organisation;

Clinical evidence tables for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Boraas, C. M., Achilles, S. L., Cremer, M. L., Chappell, C. A., Lim, S. E., Chen, B. A., Synthetic osmotic dilators with adjunctive misoprostol for same-day dilation and evacuation: a randomized controlled trial, Contraception, 94, 467-472, 2016 **Ref Id** 771039 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To compare the additional effect of buccal misoprostol to	**Sample size** n=42 assessed for eligibility (n=2 did not meet inclusion criteria; n=1 met inclusion criteria; n=9 declined participation; n=1 not offered participation) n=29 randomised (n=14 misoprostol; n=15 placebo) **Characteristics** Age in years (mean; standard deviation in parentheses): Misoprostol=28 (7.2) Placebo=25.8 (7.5) Gestational age in weeks (mean; standard deviation in parentheses): Misoprostol=19.1 (1.6) Placebo=19.0 (1.6) Parous (number; percentage in parentheses): Misoprostol=8 (57.1)	All women received a cervical block (with 10ml of 1% lidocaine or 0.25% bupivacaine) prior to insertion of Dilapan-S; the dilators were inserted a minimum of 4 hours pre-operatively. The number of dilators used at each gestational age were: 2 dilators (±1) at $<17^{+0}$ weeks, 3 dilators (±1) at 17^{+0} to 18^{+6} weeks, 4 dilators (±1) at 19^{+0} to 19^{+6} weeks, and 5 dilators (±1) at $\geq 20^{+0}$ weeks. All women also received antibiotic prophylaxis with 200mg doxycycline (administered IV at 1 study centre and oral at the other study centre). A questionnaire was administered immediately pre-operatively to assess side effects of cervical preparation. D&E was performed either under deep sedation with propofol and cervical block or	**Outcome: Baseline cervical dilation (French catheter measurement [converted to mm])** Misoprostol: N=14, M=52.8 [17.6], SD=19.8 [6.6] Placebo: N=15, M=51.4 [17.1], SD=12.0 [4.0] **Outcome: Cervical trauma (cervical lacerations)** Misoprostol: 1/14 Placebo: 3/15 **Outcome: Patient acceptability** Satisfied with priming Misoprostol: 10/14 Placebo: 14/15	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated blocks of 2, 4 and 6 by 3rd party Allocation concealment: low risk, sequentially numbered opaque envelopes prepared by independent statistician Blinding of participants and personnel: low risk, double-blind Blinding of outcome assessment: low risk, double-blind and blinded analysis performed by statistician Attrition: low risk for all outcomes. All women treated per protocol and there was no missing data

Study details	Participants	Interventions	Outcomes and Results	Comments
synthetic osmotic dilators for cervical preparation prior to same-day surgical termination of pregnancy in the second trimester **Study dates** October 2013 - March 2014 **Source of funding** Society of Family Planning Research Fund.	Placebo=10 (66.7) Nulliparous (number; percentage in parentheses): Misoprostol=6 (42.9) Placebo=5 (33.3) Prior vaginal delivery (number; percentage in parentheses): Misoprostol=5 (35.7) Placebo=8 (53.3) No prior vaginal delivery (number; percentage in parentheses): Misoprostol=9 (64.3) Placebo=7 (46.7) BMI kg/m2 (mean; standard deviation in parentheses): Misoprostol=26.3 (6.1) Placebo=30.2 (7.8) **Inclusion criteria** Women aged 18 years and above undergoing dilatation and evacuation (D&E); English speaking; pregnancy between 16^{+0} and 20^{+6} weeks' gestation on day of D&E. Willing to participate and give informed consent. **Exclusion criteria** Pregnant with multiples; allergy to misoprostol; active bleeding disorder or	800g ibuprofen and cervical block, according to standard practice at each study centre, and the procedure was carried out under ultrasound guidance. **Misoprostol + osmotic dilators:** Buccal administration of 4 misoprostol tablets (400micrograms; mcg) 3 hours prior to planned D&E. **Placebo + osmotic dilators:** Buccal administration of 4 folic acid tablets (4mg) 3 hours prior to planned D&E.	<u>Dissatisfied with priming</u> Misoprostol: 1/14 Placebo: 1/15 **Outcome: Duration of procedure in minutes (first instrument in to last out)** Misoprostol: N=14, M=11.1, SD=5.4 Placebo: N=15, M=13.5, SD=4.0	Selective reporting: low risk, all outcomes stated in method reported sufficiently **Other information** Study underpowered (at 80% with two-sided α=0.05) to detect a 4 minute difference between arms because the study was closed early due to complications.

Study details	Participants	Interventions	Outcomes and Results	Comments
	anticoagulation; signs of infection; cervical insufficiency			
Full citation Borgatta,L., Roncari,D., Sonalkar,S., Mark,A., Hou,M.Y., Finneseth,M., Vragovic,O., Mifepristone vs. osmotic dilator insertion for cervical preparation prior to surgical abortion at 14-16 weeks: a randomized trial, Contraception, 86, 567-571, 2012 **Ref Id** 278926 **Country/ies where the study was carried out** USA **Study type** Randomised controlled non-inferiority trial **Aim of the study** To determine whether mifepristone taken the day before a surgical termination results in comparable cervical priming to that achieved with osmotic dilators	**Sample size** n=107 screened for eligibility (n=21 not eligible; n=24 declined to participate; n=12 other reasons [not specified]) n=50 randomised (n=25 mifepristone; n=25 osmotic dilators) n=50 received cervical preparation per protocol (n=25 mifepristone; n=25 osmotic dilators) **Characteristics** Age in years (mean; standard deviation in parentheses): Mifepristone: 24 (5) Osmotic dilators: 25 (6) **Inclusion criteria** Women aged 18 to 45 years requesting a termination between 14 and 16 weeks' gestation. **Exclusion criteria** Fetal demise, ruptured membranes or spontaneous abortion; active substance abuse; did not speak English or Spanish.	All women received cervical priming (according to study arm) and were asked to return 20-24 hours later. A short questionnaire was completed regarding symptoms occurring overnight. A cervical block of 20ml of 1% buffered lidocaine with 4U vasopressin was given to all women at the start of the surgical procedure. If a 14mm suction cannula passed, the termination was completed using suction and forceps; if the cannula didn't pass, additional mechanical dilation was performed as required. **Mifepristone:** Women received 200mg oral mifepristone; no antibiotics or other medications were observed. **Osmotic dilators:** Women were given 60mg IM ketorolac or 800mg oral ibuprofen. The cervix was cleansed with a povidone-iodine solution and infiltrated with 10ml of 1% lidocaine then 3 to 6 dilators (based on clinician preference; either	**Outcome: Baseline cervical dilation (14mm cannula passed without additional dilation)** Mifepristone: 1/25 Osmotic dilators: 18/24 **Outcome: Pre-operative expulsion** Mifepristone: 0/25 Osmotic dilators: 1/25 **Outcome: Ease of procedure** Rated as difficult Mifepristone: 6/25 Osmotic dilators: 2/24 Rated as easy or very easy Mifepristone: 9/25 Osmotic dilator: 11/24 **Outcome: Duration of procedure** Measured as time (in minutes) from speculum in to speculum out	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated blocks between 6 and 10 Allocation concealment: low risk, sequentially numbered opaque vials Blinding of participants and personnel: no blinding; low risk for objective outcomes; high risk for subjective outcomes Blinding of outcome assessment: no blinding; low risk for objective outcomes; high risk for subjective outcomes Attrition: low risk for all outcomes; all women treated per protocol and there was no missing data Selective reporting: moderate risk, all outcomes stated in method reported but full data was not reported for baseline cervical dilation, or ease of procedure **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
Study dates October 2009 - March 2011 **Source of funding** Society of Family Planning Research Fund		laminaria or Dilapan) were inserted followed by 200mg oral doxycycline.	Mifepristone: N=25, M=9.87, SD=2.94 Osmotic dilators: N=24, M=8.00, SD=5.59 Measured as time (in minutes) from starting suction to speculum out Mifepristone: N=25, M=5.10, SD=2.86 Osmotic dilators: N=24, M=4.90, SD=2.58 **Outcome: Patient acceptability (would prefer the same method again if they had another procedure)** Mifepristone: N=24/25 Osmotic dilators: N=7/24	
Full citation Carbonell, J. L., Gallego, F. G., Llorente, M. P., Bermudez, S. B., Sala, E. S., Gonzalez, L. V., Texido, C. S., Vaginal vs. sublingual misoprostol with mifepristone for cervical priming in second-trimester abortion by dilation and evacuation: a randomized	**Sample size** n=1005 screened for eligibility (n=45 declined to participate; n=60 lived too far from clinic) n=900 randomised (n=225 mifepristone + sublingual misoprostol; n=225 mifepristone + vaginal misoprostol; n=225 sublingual	All women received misoprostol 1.5 to 2.5 hours prior to surgical termination and the cervix was assessed. Baseline cervical dilation was measured as the largest Hegar dilator that could pass without resistance and the dilation and evacuation was performed using Finks and MacKlintosh forceps and	**Outcome: Baseline cervical dilation (mm)** Mifepristone + sublingual misoprostol: N=221, M=12.6, SD=2.1 Mifepristone + vaginal misoprostol: N=220, M=12.4, SD=3.3	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated (MEDSTAT)

Study details	Participants	Interventions	Outcomes and Results	Comments
clinical trial, Contraception, 75, 230-7, 2007 **Ref Id** 771045 **Country/ies where the study was carried out** Spain **Study type** Randomised controlled trial **Aim of the study** To determine the additional cervical priming efficacy of mifepristone to sublingual or vaginal misoprostol prior to dilatation and evacuation for termination of pregnancy between 12 and 20 weeks' gestation **Study dates** July 2004 to February 2006 **Source of funding** Clínica Mediterrania Médica, Valencia, Spain	misoprostol only; n=225 vaginal misoprostol only) n=891 received misoprostol; included in analysis of misoprostol side effects (n=221 mifepristone + sublingual misoprostol [n=1 pre-operative expulsion; n=3 did not return to clinic the following day]; n=220 mifepristone + vaginal misoprostol [n=1 pre-operative expulsion; n=4 did not return to clinic the following day]; n=225 sublingual misoprostol; n=225 vaginal misoprostol) n=858 received D&E; per protocol analysis with no missing data (n=212 mifepristone + sublingual misoprostol [n=10 pre-operative expulsion; n=3 did not return to clinic the following day]; n=214 mifepristone + vaginal misoprostol [n=7 pre-operative expulsion; n=4 did not return to clinic the following day]; n=216 sublingual misoprostol [n=8 violation of protocol waiting time between misoprostol and surgery; n=1 pre-operative expulsion]; n=217 [n=6 violation of protocol waiting time between misoprostol and surgery; n=2 pre-operative expulsion]	aspiration with a no. 8 cannula; this was followed by examination curettage and 400mcg rectal misoprostol. A control ultrasound was performed 30 minutes after the surgery and were given 8 capsules of 100mg doxycycline (to be taken every 12 hours for 4 days), methylergonovine (0.25mg to be taken every 8 hours for 2 days) and, for those with gestational age >15 weeks, cabergoline (0.5mg every 12 hours for two doses) to inhibit lactation. 24 hours later women were contacted by phone to check general condition and a further ultrasound was performed after 15 days. **Mifepristone + sublingual misoprostol:** 200mg oral mifepristone was given 2 days before the termination and 48 hours before 600mcg (3 200mcg tablets) sublingual misoprostol, which was given 1.5 to 2.5 hours before termination; if cervical preparation was inadequate at the time of misoprostol administration, 1 or 2 osmotic dilators (Dilapan) were inserted.	Sublingual misoprostol: N=217, M=8.9, SD=3.0 Vaginal misoprostol: N=219, M=8.1, SD=3.3 **Outcome: Pre-operative expulsion:** Mifepristone + sublingual misoprostol: 10/225 Mifepristone + vaginal misoprostol: 7/225 Sublingual misoprostol: 1/225 Vaginal misoprostol: 2/225 **Outcome: Duration of procedure in minutes (time from anaesthesia to speculum removal)** Mifepristone + sublingual misoprostol: N=221, M=11.9, SD=4.3 Mifepristone + vaginal misoprostol: N=220, M=12.3, SD=5.0 Sublingual misoprostol: N=217, M=13.0, SD=5.3	Allocation concealment: low risk, numbered sealed opaque envelopes Blinding of participants and personnel: no blinding; low risk for objective outcomes; high risk for subjective outcomes Blinding of outcome assessment: no blinding; low risk for objective outcomes; high risk for subjective outcomes Attrition: low risk for all outcomes; total 5% and numbers/reasons for drop-out comparable across arms Selective reporting: low risk, all outcomes stated in method reported in sufficient detail **Other information** Indirectness: serious - population; includes women with gestational age from 2 weeks lower than population of interest for this question

Study details	Participants	Interventions	Outcomes and Results	Comments
	Characteristics Age in years (mean; standard deviation in parentheses): Mifepristone + sublingual misoprostol: 26.7 (7.3) Mifepristone + vaginal misoprostol: 26.6 (6.9) Sublingual misoprostol: 25.5 (6.9) Vaginal misoprostol: 25.6 (6.7) Gestational age in weeks (mean; standard deviation in parentheses): Mifepristone + sublingual misoprostol: 15.2 (2.6) Mifepristone + vaginal misoprostol: 15.7 (2.4) Sublingual misoprostol: 15.3 (2.7) Vaginal misoprostol: 15.1 (2.4) Parous (number; percentage in parentheses): Mifepristone + sublingual misoprostol: 105 (47.5) Mifepristone + vaginal misoprostol: 91 (41.4) Sublingual misoprostol: 99 (45.6) Vaginal misoprostol: 113 (51.6) Previous caesarean section (number; percentage in parentheses):	**Mifepristone + vaginal misoprostol:** 200mg oral mifepristone was given 2 days before the termination and 48 hours before 600mcg (3 200mcg tablets) vaginal misoprostol, which was given 1.5 to 2.5 hours before termination; if cervical preparation was inadequate at the time of misoprostol administration, 1 or 2 osmotic dilators (Dilapan) were inserted. **Sublingual misoprostol:** 600mcg (3 200mcg tablets) sublingual misoprostol was given 1.5 to 2.5 hours before termination **Vaginal misoprostol:** 600mcg (3 200mcg tablets) vaginal misoprostol was given 1.5 to 2.5 hours before termination	Vaginal misoprostol: N=219, M=13.0, SD=6.2	

Study details	Participants	Interventions	Outcomes and Results	Comments
	Mifepristone + sublingual misoprostol: 17 (7.6) Mifepristone + vaginal misoprostol: 14 (6.2) Sublingual misoprostol: 15 (6.7) Vaginal misoprostol: 14 (6.2) **Inclusion criteria** Women who wanted a voluntary termination between 12 and 20 weeks' gestation (biparietal diameter measured by ultrasound between 20 and 46mm, corresponding to 12.2 to 19.9 weeks) and were willing to abstain from sexual intercourse for 14 days after the termination **Exclusion criteria** Haemoglobin <9mg/dL; blood pressure >160/90 mmHg; uterine bleeding; genital infection; intolerance or allergy to mifepristone and/or misoprostol			
Full citation Casey, F. E., Ye, P. P., Perritt, J. D., Moreno-Ruiz, N. L., Reeves, M. F., A randomized controlled trial evaluating same-day mifepristone and misoprostol compared to misoprostol alone for cervical preparation prior to second-	**Sample size** n=106 assessed for eligibility (n=4 did not meet inclusion criteria; n=2 declined to participate) n=100 randomised (n=50 mifepristone; n=50 placebo)	All women provided informed consent, completed an intake form and then took the study medication (mifepristone or placebo) orally; this was followed by 400 mcg vaginal misoprostol within 15 minutes approximately 4 to 6 hours prior to scheduled procedure. D&E	**Outcome: Baseline cervical dilation (mm)** Mifepristone: N=48, M=11.7, SD=2.96 Placebo: N=48, M=10.9, SD=2.96	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated by independent research staff

Study details	Participants	Interventions	Outcomes and Results	Comments
trimester surgical abortion, Contraception, 94, 127-33, 2016 **Ref Id** 771047 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To evaluate the additional cervical priming effect of oral mifepristone to vaginal misoprostol prior to second trimester dilatation and evacuation (D&E) **Study dates** February 2013 - January 2014 **Source of funding** Society of Family Planning Research Fund	n=96 per protocol (n=48 mifepristone [n=1 declined medication; n=1 pregnancy expelled prior to D&E]; n=50 placebo [n=1 declined medication; n=1 cancelled D&E]) **Characteristics** Age in years 18-24 (number; percentage in parentheses): Mifepristone=17 (35) Placebo=23 (48) Age in years 25-29 (number; percentage in parentheses): Mifepristone=10 (21) Placebo=10 (21) Age in years 30-34 (number; percentage in parentheses): Mifepristone=11 (23) Placebo=6 (13) Age in years >35 (number; percentage in parentheses): Mifepristone=10 (21) Placebo=9 (19) Gestational age in weeks: 14^{+0} to 16^{+6} (number; percentage in parentheses): Mifepristone=16 (33) Placebo=16 (33) Gestational age in weeks: 17^{+0} to 19^{+6} (number; percentage in parentheses):	was completed according to clinic protocol; the cervix was prepared with antiseptic solution and placement of a paracervical block, a speculum was placed and cervical dilation was assessed by the largest Hegar dilator that could pass without resistance. The D&E was then performed using ring, Bierer or Sopher forceps under ultrasound guidance. **Mifepristone + misoprostol:** 200mg oral mifepristone **Placebo + misoprostol:** Identical in appearance, taste and smell to mifepristone	**Outcome: Cervical injury** Mifepristone: 0/48 Placebo: 0/48 **Outcome: Uterine perforation** Mifepristone: 0/48 Placebo: 0/48 **Outcome: Pre-operative expulsion** Mifepristone: 1/49 Placebo: 0/48 **Outcome: Ease of procedure (the procedure was easy to perform overall: agree/strongly agree)** Mifepristone: 42/48 Placebo: 40/47 **Outcome: Patient acceptability** I would choose this method again: agree/strongly agree Mifepristone: 45/48 Placebo: 44/47	Allocation concealment: low risk, sequentially numbered opaque envelopes prepared by independent pharmacy staff Blinding of participants and personnel: low risk, double-blind Blinding of outcome assessment: low risk, double-blind Attrition: low risk for all outcomes; 2 women in each arm did not receive D&E; 1 woman in placebo arm declined to answer questions post-procedure so was missing data for secondary outcomes Selective reporting: low risk, all outcomes stated in method reported sufficiently **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	Mifepristone=32 (67) Placebo=32 (67) Nulliparous (number; percentage in parentheses): Mifepristone=16 (33) Placebo=22 (46) Parous (number; percentage in parentheses): Mifepristone=32 (67) Placebo=26 (54) Prior termination (number; percentage in parentheses): Mifepristone=10 (21) Placebo=10 (21) Prior caesarean section (number; percentage in parentheses): Mifepristone=14 (29) Placebo=7 (15) BMI kg/m2 below 18.5 (number; percentage in parentheses): Mifepristone=1 (2) Placebo=2 (4) BMI kg/m2 18.5-24.9 (number; percentage in parentheses): Mifepristone=22 (46) Placebo=16 (33) BMI kg/m2 above 25 (number; percentage in parentheses): Mifepristone=25 (52) Placebo=30 (63)		I would recommend this method to my friends: agree/strongly agree Mifepristone: 43/48 Placebo: 40/47 **Outcome: Duration of procedure in minutes (estimation of cervical dilation to removal of speculum)** Mifepristone: N=48, M=11.8, SD=8.88 Placebo: N=48, M=13.0, SD=8.88	

Study details	Participants	Interventions	Outcomes and Results	Comments
	Ethnicity - Caucasian (number; percentage in parentheses): Mifepristone=20 (42) Placebo=28 (58) Ethnicity - Black (number; percentage in parentheses): Mifepristone=14 (29) Placebo=13 (27) Ethnicity - Latina (number; percentage in parentheses): Mifepristone=7 (15) Placebo=2 (4) Ethnicity - Asian or Pacific Islander (number; percentage in parentheses): Mifepristone=2 (4) Placebo=2 (4) **Inclusion criteria** Women aged over 18 years requesting non-urgent D&E between 14 and 19^{+6} weeks' gestation **Exclusion criteria** Emergent need for D&E; fetal demise; allergy or contraindication to mifepristone or misoprostol			
Full citation Drey, E. A., Benson, L. S., Sokoloff, A., Steinauer, J. E.,	**Sample size**	D&E was performed over 2-days; on the first day women received counselling, medical evaluation and placement of	**Outcome: Cervical trauma - lacerations requiring suturing**	**Limitations** **Quality of study:**

Study details	Participants	Interventions	Outcomes and Results	Comments
Roy, G., Jackson, R. A., Buccal misoprostol plus laminaria for cervical preparation before dilation and evacuation at 21-23 weeks of gestation: A randomized controlled trial, Contraception, 89, 307-313, 2014 **Ref Id** 771052 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To describe the additional cervical priming effect of buccal misoprostol to laminaria for dilation and evacuation (D&E) between 21 and 23 weeks' gestation **Study dates** October 2003 - May 2005 **Source of funding**	n=656 assessed for eligibility (n=214 ineligible; n=246 declined participation) n=196 randomised (n=98 misoprostol; n=98 placebo) n=195 per protocol (n=97 misoprostol [n=1 pregnancy expelled prior to D&E]; n=98 placebo) **Characteristics** Age in years (mean; standard deviation in parentheses): Misoprostol: 25.2 (5.6) Placebo: 25.3 (5.9) Gestational age in weeks (mean; standard deviation in parentheses): Misoprostol: 22.2 (0.68) Placebo: 22.3 (0.62) BMI kg/m2 ≥30 (number; percentage in parentheses): Misoprostol: 25 (26) Placebo: 23 (23) Nulliparous (number; percentage in parentheses): Misoprostol: 39 (40) Placebo: 37 (38) Prior termination of pregnancy (number; percentage in parentheses): Misoprostol: 62 (63) Placebo: 69 (70)	Laminaria tents (approximately the number of gestational weeks minus 10) under paracervical block. On the second day, women were randomised to and received study medication (misoprostol or placebo) and D&E was performed after 3 to 4 hours. Women received either nurse administered moderate sedation or anaesthesiologist administered deep sedation; an atraumatic tenaculum was used to stabilise the cervix and it was prepared with a paracervical block of 20ml of 1% chloroprocaine and 5U vasopressin. Additional mechanical dilation to 55 Pratt (or greater according to surgeon preference) was performed if initial cervical dilation was deemed inadequate. **Misoprostol + osmotic dilators:** 400mcg (2 200mcg tablets) buccal misoprostol **Placebo + osmotic dilators:** 100mg (2 50mg tablets) vitamin B6 - no identical tablets to misoprostol were available so	Misoprostol: 13/97 Placebo:6/98 **Outcome: Uterine perforation** Misoprostol: 1/97 Placebo: 1/98 **Outcome: Pre-operative expulsion** Misoprostol: 1/98 Placebo: 0/98 **Outcome: Ease of procedure - rated as very or extremely difficult** Misoprostol: 12/97 Placebo: 15/98 Outcome: Duration of procedure in minutes (first aspiration/dilation to last instrument out) Misoprostol: N=97, M=10.6, SD=4.9 Placebo: N=98, M=13.1, SD=8.1	Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated Allocation concealment: low risk, sequentially numbered opaque pill containers Blinding of participants and personnel: low risk, double-blind Blinding of outcome assessment: low risk, double-blind Attrition: low risk for all outcomes, all women treated per protocol with no missing data with the exception of 1 woman who expelled pregnancy prior to D&E Selective reporting: moderate risk, all outcomes stated in method reported but insufficient data for analysis of baseline cervical dilation and patient satisfaction **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
Fellowship in Family Planning, Hellman Family Awards for Early-Career Faculty Development	Prior 2nd trimester termination of pregnancy (number; percentage in parentheses): Misoprostol: 31 (32) Placebo: 37 (40) Ethnicity - Caucasian (number; percentage in parentheses): Misoprostol: 37 (38) Placebo: 34 (35) Ethnicity - Black (number; percentage in parentheses): Misoprostol: 19 (19) Placebo: 24 (24) Ethnicity - Latina (number; percentage in parentheses): Misoprostol: 24 (25) Placebo: 26 (27) **Inclusion criteria** English and Spanish speaking women aged at least 18 years old requesting a D&E between 21^{+0} and 23^{+1} weeks' gestation **Exclusion criteria** Contraindications to misoprostol; previous uterine surgery; unable to give informed consent	women self-administered mediation in private and any woman who could visually describe misoprostol were excluded (n=0)		
Full citation Edelman, A. B., Buckmaster, J. G., Goetsch, M. F., Nichols,	**Sample size** n=138 randomised (n for each arm not reported)	Counselling and evaluation were given before the procedure in line with clinic protocols and a demographic	**Outcome: Baseline cervical dilation (French catheter**	**Limitations** **Quality of study:**

Study details	Participants	Interventions	Outcomes and Results	Comments
M. D., Jensen, J. T., Cervical preparation using laminaria with adjunctive buccal misoprostol before second-trimester dilation and evacuation procedures: a randomized clinical trial, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 194, 425-30, 2006 **Ref Id** 770841 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To determine whether the addition of buccal misoprostol to laminaria improves cervical priming before second trimester dilatation and evacuation (D&E) **Study dates** September 2002 - October 2004	n=125 ITT (n=64 osmotic dilators [n=1 no demographic/operative data; n=2 decided not to proceed with procedure; n=2 did not take study medication]; n=61 osmotic dilators + misoprostol [n=2 no demographic/operative data; n=1 woman <18; n=2 decided not to proceed with procedure; n=1 did not take study medication; n=1 study packet opened but woman decline study; n=1 woman given mifepristone instead of laminaria + misoprostol]) n=116 per protocol (n=60 osmotic dilators [n=3 forgot to take study medication; n=1 did not receive study medication]; n=56 osmotic dilators + misoprostol [n=1 woman enrolled out of sequence; n=1 did not receive study medication; n=3 reason not given] **Characteristics** Age in years (mean; standard deviation in parentheses): Osmotic dilators: 25.5 (5.7) Osmotic dilators + misoprostol: 25 (5.1)	form was completed. Deep conscious sedation was given by a certified nurse using midazolam, propofol and fentanyl through mask ventilation; no paracervical block was used but women with gestations of 17 weeks and over received 40units/1000ml saline oxytocin. All women had laminaria (size LL) placed the day before the scheduled termination; if feasible, this was limited to 1 laminaria for women with gestational age up to 15^{+6} weeks and 2 laminaria for those with gestational age ≥20^{+0} weeks but an additional dilator was placed if deemed necessary for successful retention. Baseline cervical dilation was measured by the largest dilator that passed without force prior to the procedure. The termination was performed using electric suction aspiration and traditional extraction techniques. **Osmotic dilators:** 500mg magnesium oxide (placebo) was taken bucally 60 to 90 minutes before scheduled termination	**measurement [converted to mm])** Nulliparous: Osmotic dilators: N=19, M=44.4 [14.8], SD=5.7 [1.9] Osmotic dilators + misoprostol: N=20, M=47.1 [15.7], SD=5.7 [1.9] Parous: Osmotic dilators: N=45, M=48.2 [16.1], SD=5.6 [1.9] Osmotic dilators + misoprostol: N=41, M=49.0 [16.3], SD=5.1 [1.7] **Outcome: Procedure duration in minutes (speculum in to speculum out)** Osmotic dilators: N=64, M=6.9, SD=2.5 Osmotic dilators + misoprostol: N=61, M=7.0, SD=2.8	Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated by independent investigator Allocation concealment: low risk, sequentially numbered sealed opaque envelopes Blinding of participants and personnel: low risk, double-blind Blinding of outcome assessment: low risk, double-blind Attrition: low risk for all outcomes; exclusions minimal and rates and reasons were similar between arms Selective reporting: low risk, all outcomes stated in method reported sufficiently **Other information** Indirectness: serious - population; includes women with gestational age from 1 week lower than population of interest for this question

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding No sources of funding reported	Gestational age in weeks (mean; standard deviation in parentheses): Osmotic dilators: 16.5 (1.2) Osmotic dilators + misoprostol: 16.5 (1.4) Parity (mean; standard deviation in parentheses): Osmotic dilators: 1.4 (1.1) Osmotic dilators + misoprostol: 1.4 (1.4) Previous vaginal deliveries (mean; standard deviation in parentheses): Osmotic dilators: 1.2 (1.0) Osmotic dilators + misoprostol: 1.3 (1.5) Previous caesarean deliveries (mean; standard deviation in parentheses): Osmotic dilators: 0.2 (0.5) Osmotic dilators + misoprostol: 0.3 (0.7) **Inclusion criteria** Women aged ≥18 years, English speaking, in good general health, requesting a termination between 13^{+0} weeks and 20^{+6} weeks' gestation; gestational age was confirmed by ultrasound	**Osmotic dilators + misoprostol:** 400mcg misoprostol was taken bucally 60 to 90 minutes before scheduled termination		

Study details	Participants	Interventions	Outcomes and Results	Comments
	Exclusion criteria Inability to receive deep sedation; contraindication to misoprostol			
Full citation Goldberg, A. B., Drey, E. A., Whitaker, A. K., Kang, M. S., Meckstroth, K. R., Darney, P. D., Misoprostol compared with laminaria before early second-trimester surgical abortion: a randomized trial, Obstetrics & GynecologyObstet Gynecol, 106, 234-41, 2005 **Ref Id** 771425 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To compare the cervical priming effect of overnight laminaria with same-day misoprostol prior to second trimester surgical termination **Study dates**	**Sample size** n=203 assessed for eligibility (n=72 ineligible; n=47 declined to participate) n=84 randomised (n=42 misoprostol; n=42 osmotic dilators) n=83 per protocol, included in analysis (n=41 misoprostol [n=1 did not return to clinic on day 2]; n=42 osmotic dilators) **Characteristics** Age in years (median; range in parentheses): Misoprostol: 23 (18-37) Osmotic dilators: 23 (18-39) Gestational age in days (median; range in parentheses): Misoprostol: 105 (92-112) Osmotic dilators: 104.5 (91-112) Nulliparous (number; percentage in parentheses): Misoprostol: 13 (31.7) Osmotic dilators: 13 (30.9) Prior vaginal delivery (number; percentage in parentheses): Misoprostol: 21 (51.2)	The day before the termination women underwent a pre-operative evaluation including a speculum examination, explanation of possible side effects and STI screening; women were then discharged and told to return the following day for their scheduled termination were they underwent a digital examination and received study medication (misoprostol or placebo). After 3 to 4 hours women were taken to the operating room and the non-operating physician (unblinded) removed all laminaria, sponges, and tablets, placed the speculum, and prepared the cervix with povidone-iodine, per standard clinic protocol. Moderate IV sedation (fentanyl and midazolam) and a 20ml paracervical block were administered and baseline cervical dilation was measured. The termination was completed with suction curettage and forceps, if necessary, under ultrasound guidance.	**Outcome: Baseline cervical dilation (French catheter measurement [converted to mm])** Misoprostol: N=41, M=33 [11], SD=7.1 [2.4] Osmotic dilators: N=42, M=43 [14.3], SD=7.9 [2.6] **Outcome: Cervical trauma** Misoprostol: 2/41 Osmotic dilators: 0/42 **Outcome: Uterine perforation** Misoprostol: 1/41 Osmotic dilators: 0/42 **Outcome: Ease of procedure** Not difficult: Misoprostol: 15/41 Osmotic dilators: 29/42 Mildly difficult:	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated blocks prepared by independent researcher Allocation concealment: low risk, sequentially numbered opaque envelopes Blinding of participants and personnel: low risk, double-blind Blinding of outcome assessment: low risk, double-blind Attrition: low risk for all outcomes Selective reporting: moderate risk, all outcomes stated in method reported but insufficient detail presented for analysis of procedure duration **Other information** Indirectness: serious - population; includes women

Study details	Participants	Interventions	Outcomes and Results	Comments
February 2002 - September 2003 **Source of funding** University of California San Francisco Center for Reproductive Health Research and Policy	Osmotic dilators: 22 (52.4) Prior caesarean delivery (number; percentage in parentheses): Misoprostol: 9 (21.9) Osmotic dilators: 11 (26.2) Prior induced termination (number; percentage in parentheses): Misoprostol: 23 (56.1) Osmotic dilators: 31 (73.8) Race - Caucasian (number; percentage in parentheses): Misoprostol: 4 (9.8) Osmotic dilators: 5 (11.9) Race - Black (number; percentage in parentheses): Misoprostol: 23 (56.1) Osmotic dilators: 15 (35.7) Race - Latina (number; percentage in parentheses): Misoprostol: 12 (29.3) Osmotic dilators: 18 (42.9) Race - Asian (number; percentage in parentheses): Misoprostol: 1 (2.4) Osmotic dilators: 4 (9.5) **Inclusion criteria** English or Spanish speaking women aged ≥18 years who were in good general health	**Misoprostol:** Following the digital examination prior to the termination, 400mcg (2 200mcg tablets) misoprostol was placed in the posterior fornix of the vagina; tablets were moistened with 2 to 3 drops of saline before insertion. **Osmotic dilators:** During the pre-operative examination, a 10ml chloroprocaine paracervical block was administered and 3 to 6 medium laminaria (4mm size) were placed. Following the digital examination prior to the termination, 2 vitamin B6 tablets (placebo) were placed in the posterior fornix of the vagina; tablets were moistened with 2 to 3 drops of saline before insertion.	Misoprostol: 15/41 Osmotic dilators: 10/42 <u>Moderate/markedly difficult:</u> Misoprostol: 11/41 Osmotic dilators: 2/42 **Outcome: Patient acceptability** <u>Would choose same cervical priming method again:</u> Misoprostol: 38/41 Osmotic dilators: 26/42 <u>Would prefer 1-day procedure with misoprostol over 2-day procedure with laminaria:</u> Misoprostol: 36/41 Osmotic dilators: 32/42	with gestational age from 1 week lower than population of interest for this question

Study details	Participants	Interventions	Outcomes and Results	Comments
	and decided to have an outpatient termination between 12^{+6} weeks and 15^{+6} weeks' gestation (confirmed by ultrasound) **Exclusion criteria** >1 previous caesarean delivery; multiple gestations; fetal demise (confirmed by ultrasound); cervical or lower uterine segment myoma >3cm in diameter; prior cone biopsy or loop electrosurgical excision procedure; bleeding disorder or current anticoagulation treatment; IUD in place; allergy to misoprostol; breastfeeding and unwilling to temporarily discard milk			
Full citation Goldberg, A. B., Fortin, J. A., Drey, E. A., Dean, G., Lichtenberg, E. S., Bednarek, P. H., Chen, B. A., Dutton, C., McKetta, S., Maurer, R., Winikoff, B., Fitzmaurice, G. M., Cervical Preparation Before Dilation and Evacuation Using Adjunctive Misoprostol or Mifepristone Compared With Overnight Osmotic Dilators Alone: A Randomized Controlled Trial, Obstetrics &	**Sample size** n=543 screened for eligibility (n=190 declined to participate; n=50 did not meet inclusion criteria; n=3 other reasons) n=300 randomised (n=100 osmotic dilators alone; n=100 osmotic dilators + misoprostol; n=100 osmotic dilators + mifepristone) n=298 received allocated intervention (n=99 osmotic dilators alone [n=1 woman withdrew];n =100 osmotic dilators + misoprostol; n=99	On the 1st day, research staff confirmed gestational age by ultrasound and received mifepristone or placebo depending on study arm. Within 30 minutes of medication, all women underwent osmotic dilator insertion with laminaria and/or Dilapan-S according to standard protocol at each study centre; number and mix of dilators was at discretion of treating physician. On the second day, women received misoprostol or placebo	**Outcome: Baseline cervical dilation (cm)** Osmotic dilators alone: N=99, M=2.2, SD=0.5 Osmotic dilators + misoprostol: N=97, M=2.5, SD=0.9 Osmotic dilators + mifepristone: N=98, M=2.4, SD=0.5	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated blocks of 6 Allocation concealment: low risk, sequentially numbered opaque envelopes prepared by independent staff

Study details	Participants	Interventions	Outcomes and Results	Comments
GynecologyObstet Gynecol, 126, 599-609, 2015 **Ref Id** 771426 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To evaluate differences in dilatation and evacuation (D&E) procedure time with osmotic dilators alone compared with osmotic dilators and misoprostol or mifepristone **Study dates** February 2013 - February 2014 **Source of funding** Society of Family Planning Research Fund	osmotic dilators + mifepristone [n=1 woman ineligible]) n=295 included in analysis (n=99 osmotic dilators alone; n=98 osmotic dilators + misoprostol [n=1 D&E not completed on first attempt; n=1 pre-operative expulsion]; n=98 osmotic dilators + mifepristone [n=1 D&E not completed on first attempt])* **Characteristics** Age in years (mean; standard deviation in parentheses): Osmotic dilators alone: 24.6 (5.7) Osmotic dilators + misoprostol: 25.9 (5.9) Osmotic dilators + mifepristone: 25.3 (5.8) Gravidity (median; IQR in parentheses): Osmotic dilators alone: 2 (1-4) Osmotic dilators + misoprostol: 3 (2-5) Osmotic dilators + mifepristone: 3 (2-5) Parity (median; IQR in parentheses): Osmotic dilators alone: 1 (0-2) Osmotic dilators + misoprostol: 1 (0-2)	depending on study arm; terminations began 3 hours (± 30 minutes) after medication and were completed according to standard protocol at each study centre. **Osmotic dilators only:** Oral placebo taken on day 1 and buccal placebo held bucally for 30 minutes (then any remaining fragments swallowed) on day 2 **Osmotic dilators + misoprostol:** Oral placebo taken on day 1 and 400mcg buccal misoprostol held bucally for 30 minutes (then any remaining fragments swallowed) on day 2 **Osmotic dilators + mifepristone:** 200mg oral mifepristone taken on day 1 and buccal placebo held bucally for 30 minutes (then any remaining fragments swallowed) on day 2	**Outcome: Cervical trauma (laceration requiring suturing)** Osmotic dilators alone: 3/99 Osmotic dilators + misoprostol: 0/100 Osmotic dilators + mifepristone: 0/99 **Outcome: Uterine perforation** Osmotic dilators alone: 0/99 Osmotic dilators + misoprostol: 1/99 Osmotic dilators + mifepristone: 0/98 **Outcome: Pre-operative expulsion** Osmotic dilators alone: 0/99 Osmotic dilators + misoprostol: 1/100 Osmotic dilators + mifepristone: 0/99 **Outcome: Ease of procedure - difficult or very difficult** Osmotic dilators alone: 15/99	Blinding of participants and personnel: low risk, double-blind Blinding of outcome assessment: low risk, double-blind Attrition: low risk for all outcomes Selective reporting: moderate risk, all outcomes stated in method reported but insufficient detail for analysis for duration of procedure (including management of complications) and for subgroup analysis based on parity **Other information** * Numbers included in analysis reported in study flow diagram did not match the number of women in reported analyses

Study details	Participants	Interventions	Outcomes and Results	Comments
	Osmotic dilators + mifepristone: 1 (0-2) Prior vaginal delivery (number; percentage in parentheses): Osmotic dilators alone: 48 (48) Osmotic dilators + misoprostol: 59 (59) Osmotic dilators + mifepristone: 56 (56) Prior caesarean delivery (number; percentage in parentheses): Osmotic dilators alone: 13 (13) Osmotic dilators + misoprostol: 14 (14) Osmotic dilators + mifepristone: 17 (17) Ethnicity - Caucasian (number; percentage in parentheses): Osmotic dilators alone: 31 (31) Osmotic dilators + misoprostol: 22 (22) Osmotic dilators + mifepristone: 29 (29) Ethnicity - African American/Black (number; percentage in parentheses): Osmotic dilators alone: 39 (39) Osmotic dilators + misoprostol: 48 (48) Osmotic dilators + mifepristone: 36 (36)		Osmotic dilators + misoprostol: 11/99 Osmotic dilators + mifepristone: 3/98 **Outcome: Patient acceptability** <u>Satisfied or very satisfied with cervical preparation</u> Osmotic dilators alone: 72/99 Osmotic dilators + misoprostol: 80/100 Osmotic dilators + mifepristone: 80/99 <u>Dissatisfied or very dissatisfied with cervical preparation</u> Osmotic dilators alone: 6/99 Osmotic dilators + misoprostol: 4/100 Osmotic dilators + mifepristone: 4/99 **Outcome: Duration of procedure (first instrument in to last instrument out; excluding measurement of baseline cervical dilation)**	

Study details	Participants	Interventions	Outcomes and Results	Comments
	Ethnicity - Hispanic/Latina (number; percentage in parentheses): Osmotic dilators alone: 19 (19) Osmotic dilators + misoprostol: 18 (18) Osmotic dilators + mifepristone: 22 (22) **Inclusion criteria** English or Spanish speaking women added 18 years and over that were requesting and eligible for an outpatient between 16^{+0} and 23^{+6} weeks' gestation **Exclusion criteria** Women who were incarcerated; spontaneous fetal demise; chorioamnionitis; active heavy bleeding or hemodynamic instability; active labour or cervical insufficiency; allergy or contraindication to mifepristone or misoprostol		Osmotic dilators alone: N=99, M=6.27, SD=3.5 Osmotic dilators + misoprostol: N=98, M=6.28, SD=4.6 Osmotic dilators + mifepristone: N=98, M=5.53, SD=2.9	
Full citation Grossman, D., Constant, D., Lince-Deroche, N., Harries, J., Kluge, J., A randomized trial of misoprostol versus laminaria before dilation and evacuation in South Africa,	**Sample size** n=240 assessed for eligibility (n=21 <18 years old; n=9 >1 caesarean section; n=4 multiple gestation; n=3 beyond gestational limit for study; n=1 could not speak any of the Study languages; n=1	The day before the scheduled termination all women underwent a speculum examination to screen for cervicitis. All women were given prophylactic antibiotics (100mg doxycycline to be taken twice daily and 400mg metronidazole	**Outcomes: Uterine perforation (suspected):** Osmotic dilators: 0/78 Misoprostol: 1/78	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated

Study details	Participants	Interventions	Outcomes and Results	Comments
Contraception, 90, 234-41, 2014 **Ref Id** 771057 **Country/ies where the study was carried out** South Africa **Study type** Randomised controlled trial **Aim of the study** To compare the cervical priming effect of buccal misoprostol with laminaria prior to second trimester dilation and evacuation (D&E) for termination of pregnancy **Study dates** May 2012 - June 2013 **Source of funding** Society of Family Planning; World Health Organization; South African Medical Research Council	diagnosed with cervicitis; n=19 not interested due to work or school commitments; n=23 not interested due to study specifics) n=159 randomised (n=79 osmotic dilators; n=80 misoprostol) n=156 received cervical priming (n=78 osmotic dilators [n=1 did not tolerate laminaria insertion]; n=78 misoprostol [n=1 withdrew from study; n=1 decided to continue pregnancy]) n=155 with complete follow-up data (n=78 osmotic dilators; n=77 misoprostol) **Characteristics** Age in years (mean) Osmotic dilators: 27.9 Misoprostol: 26.5 Gestational age in weeks (mean) Osmotic dilators: 14.7 Misoprostol: 15.0 Nulliparous (number; percentage in parentheses): Osmotic dilators: 17 (21.8) Misoprostol: 23 (29.5) Parity=1 (number; percentage in parentheses): Osmotic dilators: 24 (30.8)	3 times daily beginning immediately) and 400mg ibuprofen to be taken as needed (up to 3 times a day) and were asked to return at 7am the following day. A paracervical block of 20ml of 1% lidocaine was administered at the start of the D&E, which was performed with manual vacuum aspiration and forceps. Women were scheduled for a follow-up visit 7 days later and were contacted by telephone if they did not attend. **Osmotic dilators:** The day before the termination women received a paracervical block of 12ml of 1% lidocaine and 3 to 7 laminaria (3 to 5mm) were inserted depending on gestational age (13^{+0} to 13^{+6} , 2 to 3; 14^{+0} to 15^{+6}, 3 to 4; 16^{+0} to 16^{+6}, 4 to 5; 17^{+0} to 17^{+6}, 5 to 6; 18^{+0} to 18^{+6}, 5 to 7; 19^{+0}, 6 to 8). Laminaria were removed the next day by a study nurse to maintain blinding of the physician performing the D&E). **Misoprostol:** The day before the termination women were given 400mcg (2	**Outcome: Pre-operative expulsion:** Osmotic dilators: 0/78 Misoprostol: 2/78 **Outcome: Duration of procedure in minutes (speculum in to speculum out)** <u>Nulliparous</u> Osmotic dilators: N=23, M=13.6, SD=NR Misoprostol: N=17, M=13.8, SD=NR p=0.899, SE=1.565 <u>Parous</u> Osmotic dilators: N=55, M=12.6, SD=NR Misoprostol: N=61, M=12.1, SD=NR p=0.666, SE=1.155	random permuted blocks between 4 and 8; prepared by independent researcher Allocation concealment: low risk, sequentially numbered opaque envelopes Blinding of participants and personnel: no blinding of women, partial blinding of physicians (blind to allocation unless the study nurse had difficulty removing laminaria; number of events not reported); low risk for objective outcomes; high risk for participant-reported subjective outcomes; unclear risk for physician-reported subjective outcomes Blinding of outcome assessment: no blinding of women, partial blinding of physicians; low risk for objective outcomes; high risk for participant-reported subjective outcomes; unclear risk for physician-reported subjective outcomes Attrition: low risk for all outcomes; only 3 women were excluded following randomisation and only 1 woman (misoprostol arm) was missing follow-up data Selective reporting: moderate risk, patient acceptability

Study details	Participants	Interventions	Outcomes and Results	Comments
	Misoprostol: 29 (37.2) Parity=2 (number; percentage in parentheses): Osmotic dilators: 24 (30.8) Misoprostol: 14 (17.9) Parity≥3 (number; percentage in parentheses): Osmotic dilators: 13 (16.7) Misoprostol: 12 (15.3) Prior caesarean section (number; percentage in parentheses): Osmotic dilators: 5 (6.4) Misoprostol: 8 (10.3) Prior termination (number; percentage in parentheses): Osmotic dilators: 10 (12.8) Misoprostol: 13 (16.7) Race - African (number; percentage in parentheses): Osmotic dilators: 48 (61.5) Misoprostol: 41 (52.6) Race - Caucasian (number; percentage in parentheses): Osmotic dilators: 1 (1.3) Misoprostol: 0 (0.0) **Inclusion criteria** Women aged ≥18 years old, able to speak English, Afrikaans or Xhosa, with a gestation between 13^{+0} and	200mcg tablets) misoprostol and instructed to administer them bucally at home at 5am the next morning and to swallow any remains after 30 minutes. Women were examined around 8am and were given an additional dose of 400mcg buccal misoprostol if pain and bleeding were absent or mild (with discretion from the study nurse) and waited at least another hour before the D&E; those with gestational age greater than 18^{+0} weeks were reassessed at 10am and a third dose of 400mcg buccal misoprostol was permitted if required.		reported to be high and similar between arms but data is not presented **Other information** Indirectness: serious - population; includes women with gestational age from 1 week lower than population of interest for this question Study underpowered (at 80% with 2-sided α=0.05) to detect difference in primary outcome (pre-operative expulsion)

Study details	Participants	Interventions	Outcomes and Results	Comments
	19^{+0} weeks on the day of D&E. They needed to be staying within an hour of the hospital the night before the termination and be contactable by telephone. **Exclusion criteria** Active cervicitis; multiple gestation; fetal demise; history of bleeding disorder or current anticoagulation treatment; allergic to misoprostol; more than one prior caesarean; breastfeeding and unable/unwilling to temporarily discard milk			
Full citation Newmann, S. J., Sokoloff, A., Tharyil, M., Illangasekare, T., Steinauer, J. E., Drey, E. A., Same-day synthetic osmotic dilators compared with overnight laminaria before abortion at 14-18 weeks of gestation: a randomized controlled trial, Obstetrics & GynecologyObstet Gynecol, 123, 271-8, 2014 **Ref Id** 771435	**Sample size** n=178 screened for eligibility (n=95 decline to participate; n=11 did not meet inclusion criteria) n=72 randomised (n=36 same-day osmotic dilators; n=36 overnight osmotic dilators) n=69 received allocated intervention; per protocol (n=34 same-day osmotic dilators [n=1 decided to continue pregnancy; n=1 rescheduled due to transportation issues]; n=35 overnight osmotic dilators [n=1 decided to continue pregnancy])	All women underwent a speculum examination the day before termination to maintain blinding. On the second day, women completed a questionnaire about overnight symptoms and underwent a second speculum examination. The termination occurred 4 to 6 hours after the speculum examination on the second day; immediately prior to this, a second questionnaire was completed to report any symptoms occurring during the day waiting. The osmotic dilators were removed by a study staff member unblinded	**Outcome: Baseline cervical duration in mm** Same-day osmotic dilators: N=34, M=48.0, SD=11.3 Overnight osmotic dilators: N=35, M=59.7; SD=10.0 **Outcome: Cervical trauma (lacerations)** Same-day osmotic dilators: 0/34 Overnight osmotic dilators: 1/35	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated permuted blocks of 4 and 6 Allocation concealment: low risk, sequentially numbered opaque envelopes prepared by independent research staff Blinding of participants and personnel: low risk, double-blind

Study details	Participants	Interventions	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** Randomised controlled noninferiority trial **Aim of the study** To determine noninferiority of same-day synthetic osmotic dilators compared with overnight laminaria osmotic dilators for cervical priming prior to second trimester surgical termination **Study dates** October 2008 - February 2010 **Source of funding** National Center for Advancing Translational Sciences and National Institutes of Health	**Characteristics** Age in years (median; IQR in parentheses): Same-day osmotic dilators: 26.5 (22.0-32.0) Overnight osmotic dilators: 21.0 (19.0-26.0) Gestational age in weeks (mean; standard deviation in parentheses): Same-day osmotic dilators: 16.6 (1.1) Overnight osmotic dilators: 16.2 (1.1) BMI kg/m2 (median; IQR in parentheses): Same-day osmotic dilators: 27.1 (23.4-31.4) Overnight osmotic dilators: 27.5 (23.6-32.6) Nulliparous (number; percentage in parentheses): Same-day osmotic dilators: 9 (26.5) Overnight osmotic dilators: 12 (34.3) Prior pregnancies (median; IQR in parentheses): Same-day osmotic dilators: 4 (2-6) Overnight osmotic dilators: 3 (2-5)	to the treatment allocation; the physician performing the D&E then measured cervical dilation, prepared the cervix was povidone-iodine and a paracervical block of 5U vasopressin. Additional dilation of the cervix was performed with Pratt dilators if needed then the termination was completed using suction and forceps under ultrasound. **Same-day osmotic dilators:** The day before termination women underwent a sham examination which included placement of sterile gauze. On the day of the termination, the gauze was removed, a paracervical block placed, synthetic dilators were inserted (2 to 3 dilators placed for those with gestational age 14^{+0} to 15^{+6}; 2 to 5 dilators for those with gestational age 16^{+0} to 18^{+0}) and 1 laminaria to facilitate removal of synthetic dilators. **Overnight osmotic dilators:** The day before termination women received a paracervical block and insertion of laminaria (mean diameter 4mm; number	**Outcome: Ease of procedure - inadequate dilation** Same-day osmotic dilators: 19/32 Overnight osmotic dilators: 7/30 **Outcome: Patient acceptability** <u>Satisfaction with termination</u> Same-day osmotic dilators: 26/34 Overnight osmotic dilators: 24/33 <u>Satisfaction with overall clinic experience</u> Same-day osmotic dilators: 25/34 Overnight osmotic dilators: 22/33 **Outcome: Duration of procedure in minutes (first instrument in to last instrument out)** <u>Whole sample</u> Same-day osmotic dilators: N=34, M=8.1, SD=5.5	Blinding of outcome assessment: low risk, double-blind Attrition: low risk for all outcomes Selective reporting: low risk, all outcomes stated in method reported sufficiently Study had inadequate power to compare complications between groups so procedure duration was chosen as a surrogate for procedural difficulty and complications. Those in the same-day group still had a two day procedure (to enable blinding) and therefore patient satisfaction may not be representative of a one-day procedure **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	Prior induced termination (number; percentage in parentheses): Same-day osmotic dilators: 22 (64.7) Overnight osmotic dilators: 22 (62.9) Prior vaginal delivery (number; percentage in parentheses): Same-day osmotic dilators: 14 (41.2) Overnight osmotic dilators: 15 (42.9) Prior caesarean delivery (number; percentage in parentheses): Same-day osmotic dilators: 11 (32.4) Overnight osmotic dilators: 9 (25.7) Ethnicity - Caucasian (number; percentage in parentheses): Same-day osmotic dilators: 8 (24.2) Overnight osmotic dilators: 4 (11.8) Ethnicity - Black (number; percentage in parentheses): Same-day osmotic dilators: 15 (45.5) Overnight osmotic dilators: 16 (47.1)	of laminaria approximately the number of weeks' gestation minus 10) followed by placement of sterile gauze. On the day of the termination, women underwent a sham examination where the gauze was replaced.	Overnight osmotic dilators: N=35, M=5.9, SD=2.9 Nulliparous Same-day osmotic dilators: N=9, M=11.4, SD=8.2 Overnight osmotic dilators: N=12, M=6.4, SD=2.4	

Study details	Participants	Interventions	Outcomes and Results	Comments
	Ethnicity - Latina (number; percentage in parentheses): Same-day osmotic dilators: 8 (24.2) Overnight osmotic dilators: 10 (29.4) Ethnicity - Asian or Pacific Islander (number; percentage in parentheses): Same-day osmotic dilators: 2 (6.1) Overnight osmotic dilators: 4 (11.8) **Inclusion criteria** English and Spanish speaking Women aged 18 years and over and were between 13^{+6} and 17^{+6} the day prior to termination **Exclusion criteria** Women who were incarcerated; known allergy to synthetic osmotic dilators of laminaria			
Full citation Sagiv, R., Mizrachi, Y., Glickman, H., Kerner, R., Keidar, R., Bar, J., Golan, A., Laminaria vs. vaginal misoprostol for cervical preparation before second-trimester surgical abortion: a	**Sample size** n=117 assessed for eligibility (n=27 ineligible; n=6 declined participation) n=84 randomised (n=41 misoprostol; n=43 osmotic dilators)	Terminations were performed under general endotracheal anaesthesia a speculum was placed and baseline cervical dilation was assessed. Ultrasound guidance was used and the procedure was completed with suction and ring forceps.	**Outcome: Baseline cervical dilation (mm)** Misoprostol: N=41, M=12.4, SD=2.7 Osmotic dilators: N=43, M=12.8, SD=1.8	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated

Study details	Participants	Interventions	Outcomes and Results	Comments
randomized clinical trial, Contraception, 91, 406-11, 2015 **Ref Id** 771079 **Country/ies where the study was carried out** Israel **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy and acceptability of misoprostol with laminaria for cervical priming prior to second trimester dilatation and evacuation **Study dates** January 2008 - January 2011 **Source of funding** No sources of funding reported	n=84 ITT (n=41 misoprostol; n=43 osmotic dilators) **Characteristics** Age in years (median; range presented in parentheses): Misoprostol: 30 (15-47) Osmotic dilators: 29 (17-45) Gestational age in weeks (median; range presented in parentheses): Misoprostol: 17 (14-20) Osmotic dilators: 16 (14-20) Nulliparous (number; percentage in parentheses): Misoprostol: 21 (51.2) Osmotic dilators: 23 (53.4) Previous vaginal delivery (number; percentage in parentheses): Misoprostol: 15 (36.5) Osmotic dilators: 18 (41.8) Previous caesarean delivery (number; percentage in parentheses): Misoprostol: 6 (14.6) Osmotic dilators: 4 (9.3) **Inclusion criteria** Women aged ≥15 in good general health requesting termination of pregnancy	**Misoprostol:** 600mcg misoprostol (3 200mcg tablets) was administered in the posterior fornix of the vagina at midnight before the termination **Osmotic dilators:** Between 1 and 6 laminaria were placed at midnight before the termination; the vagina was cleansed with aqueous Betadine solution and the laminaria were placed using a tenaculum with no paracervical anaesthesia.	**Outcome: Pre-operative expulsion** Misoprostol: 1/41 Osmotic dilators: 0/43	list prepared by independent researcher Allocation concealment: low risk, sequentially numbered opaque envelopes Blinding of participants and personnel: no blinding; low risk for objective outcomes; high risk for subjective outcomes Blinding of outcome assessment: no blinding; low risk for objective outcomes; high risk for subjective outcomes Attrition: low risk for all outcomes; no loss to follow-up or missing data Selective reporting: moderate risk, all outcomes stated in method reported but insufficient detail for analysis of duration of procedure or procedure difficulty **Other information** Indirectness: serious - population; includes women with gestational age from 1 week lower than population of interest for this question

Study details	Participants	Interventions	Outcomes and Results	Comments
	between 13 and 20 weeks' gestation **Exclusion criteria** Allergy to misoprostol; fetal demise; bleeding disorder; current anticoagulation therapy; previous loop electrosurgical excision procedure or conisation procedure; multiple-gestation; breast feeding			
Full citation Shaw, K. A., Shaw, J. G., Hugin, M., Velasquez, G., Hopkins, F. W., Blumenthal, P. D., Adjunct mifepristone for cervical preparation prior to dilation and evacuation: a randomized trial, Contraception, 91, 313-9, 2015 **Ref Id** 771083 **Country/ies where the study was carried out** USA **Study type** Randomised controlled noninferiority trial	**Sample size** n=106 screened for eligibility (n=42 did not meet inclusion criteria; n=3 declined to participate; n=11 not approached) n=50 randomised (n=24 osmotic dilators + misoprostol; n=26 osmotic dilators + misoprostol + mifepristone) n=49 received allocated intervention (n=24 osmotic dilators + misoprostol; n=25 osmotic dilators + misoprostol + mifepristone [n=1 did not return to clinic]) n=45 per protocol (n=21 osmotic dilators + misoprostol [n=2 pre-operative expulsion; n=1 unscheduled D&E]; n=24 osmotic dilators + misoprostol + mifepristone [n=1 pre-operative expulsion])	All women received 1mg intraamniotic digoxin the day prior to the termination and 400mcg buccal misoprostol 90 minutes before the termination. Osmotic dilators were removed by a nonblinded physician to maintain blinding of the surgeon performing the termination; the rest of the termination was performed by a blinded surgeon under deep sedation or general anaesthesia. A paracervical block of lidocaine and vasopressin was used and baseline cervical dilation was determined by the largest Pratt dilator that passed without difficulty; the D&E was performed using suction and standard extraction measures under ultrasound guidance.	**Outcome: Duration of procedure in minutes (first instrument in to last instrument out)** Osmotic dilators + misoprostol: N=21, M=10.93, SD=5.13 Osmotic dilators + misoprostol + mifepristone: N=24, M=11.87, SD=5.48	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated sequence with variable block size Allocation concealment: low risk, numbered opaque envelopes Blinding of participants and personnel: women unblinded, physician performing D&E blinded; low risk for objective outcomes and subjective physician-reported outcomes; high risk for subjective patient-reported outcomes Blinding of outcome assessment: women unblinded, physician performing D&E

Study details	Participants	Interventions	Outcomes and Results	Comments
Aim of the study To investigate the additional cervical priming effect of mifepristone to osmotic dilators and misoprostol before surgical termination of pregnancy after 19 weeks' gestation **Study dates** June 2012 - June 2013 **Source of funding** Society of Family Planning	**Characteristics** Age in years (mean; standard deviation in parentheses): Osmotic dilators + misoprostol: 27.6 (6.5) Osmotic dilators + misoprostol + mifepristone: 27.7 (6.7) Gestational age in weeks (mean; standard deviation in parentheses): Osmotic dilators + misoprostol: 20.8 (1.1) Osmotic dilators + misoprostol + mifepristone: 20.9 (1.2) BMI kg/m2 (mean; standard deviation in parentheses): Osmotic dilators + misoprostol: 29.0 (6.4) Osmotic dilators + misoprostol + mifepristone: 28.8 (6.9) Nulliparous (number; percentage in parentheses): Osmotic dilators + misoprostol: 3 (12) Osmotic dilators + misoprostol + mifepristone: 12 (46) Prior vaginal deliveries=0 (number; percentage in parentheses): Osmotic dilators + misoprostol: 4 (17)	**Osmotic dilators + misoprostol:** Two sets of osmotic dilators (Dilapan-S, 4mm) were placed 18 to 24 hours apart. Two days prior to the scheduled termination 2 to 4 dilators were placed after administration of a paracervical block; the day before the termination an additional 4 to 5 dilators were placed (total number 6 to 9). **Osmotic dilators + misoprostol + mifepristone:** The day prior to the scheduled termination women received 200mg mifepristone and had 4 to 5 dilators placed after administration of a paracervical block.		blinded; low risk for objective outcomes and subjective physician-reported outcomes; high risk for subjective patient-reported outcomes Attrition: low risk for all outcomes; 90% treated per protocol and no missing data for those who were treated per protocol Selective reporting: moderate risk, outcomes reported in limited detail **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	Osmotic dilators + misoprostol + mifepristone: 15 (58) Prior vaginal deliveries=1 (number; percentage in parentheses): Osmotic dilators + misoprostol: 11 (46) Osmotic dilators + misoprostol + mifepristone: 4 (15) Prior vaginal deliveries=2 (number; percentage in parentheses): Osmotic dilators + misoprostol: 3 (13) Osmotic dilators + misoprostol + mifepristone: 3 (12) Prior vaginal deliveries≥3 (number; percentage in parentheses): Osmotic dilators + misoprostol: 6 (25) Osmotic dilators + misoprostol + mifepristone: 4 (15) Prior caesarean section (number; percentage in parentheses): Osmotic dilators + misoprostol: 3 (13) Osmotic dilators + misoprostol + mifepristone: 3 (12) **Inclusion criteria**			

Study details	Participants	Interventions	Outcomes and Results	Comments
	Women fluent in English or Spanish aged >18 years presenting for outpatient termination between 19^{+0} and 23^{+6} weeks' gestation; able to give informed consent and comply with protocol **Exclusion criteria** Allergy to any study medication			
Full citation Shaw, K. A., Lerma, K., Shaw, J. G., Scrivner, K. J., Hugin, M., Hopkins, F. W., Blumenthal, P. D., Preoperative effects of mifepristone for dilation and evacuation after 19 weeks of gestation: a randomised controlled trial, 124, 1973-1981, 2017 **Ref Id** 770965 **Country/ies where the study was carried out** USA **Study type** Randomised controlled noninferiority trial	**Sample size** n=175 screened for eligibility (n=57 did not meet inclusion criteria; n=38 decline to participate) n=80 randomised (n= 28 mifepristone + misoprostol; n=28 osmotic dilators + mifepristone + misoprostol; n=24 osmotic dilators + placebo + misoprostol) n=75 per protocol (n=27 mifepristone + misoprostol [n=1 did not return to clinic]; n=27 osmotic dilators + mifepristone + misoprostol [n=1 ineligible]; n=21 osmotic dilators + placebo + misoprostol [n=1 did not return to clinic; n=1 ineligible; n=1 underwent induction termination]) Characteristics	The day prior to the scheduled termination all women received cervical preparation, according to treatment arm; those at >22 weeks' gestation also received 1mg of intra-amniotic or intra-fetal digoxin, which is standard care at the clinical sites beyond 22 weeks. On the day of the procedure, all women received 400mcg buccal misoprostol; this was given 90 minutes prior to scheduled termination for those who had osmotic dilators and 2 to 3 hours before for those who did not have osmotic dilators. A second dose of 400mcg buccal misoprostol was permitted (at the physicians discretion) if cervical dilation was <1cm (only used once). All terminations were performed using standard D&E techniques using ultrasound guidance, under deep sedation or general	**Outcome: Baseline cervical dilation ≥3cm** Mifepristone + misoprostol: 1/27 Osmotic dilators + mifepristone + misoprostol: 14/27 Osmotic dilators + placebo + misoprostol: 12/21 **Outcome: Cervical trauma (lacerations)** Mifepristone + misoprostol: 5/27 Osmotic dilators + mifepristone + misoprostol: 0/27 Osmotic dilators + placebo + misoprostol: 1/21	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: low risk, computer generated - variable block size stratified by site and gestational age Allocation concealment: low risk, numbered sealed opaque envelopes prepared by a Stanford employee not involved with the study Blinding of participants and personnel: partial blinding (blind to medication but not use of dilators for practical reasons); low risk for objective outcomes; high risk for subjective outcomes Blinding of outcome assessment: partial blinding; low risk for objective

Study details	Participants	Interventions	Outcomes and Results	Comments
Aim of the study To determine the cervical priming effect of mifepristone as an addition to, or replacement for, osmotic dilators prior to surgical termination after 19 weeks' gestation **Study dates** November 2013 - November 2015 **Source of funding** The David and Lucile Packard Foundation	Age in years (mean; standard deviation in parentheses): Mifepristone + misoprostol: 28.3 (7.0) Osmotic dilators + mifepristone + misoprostol: 27.5 (6.4) Osmotic dilators + placebo + misoprostol: 27.3 (6.1) BMI kg/m2 (mean; standard deviation in parentheses): Mifepristone + misoprostol: 26.5 (7.8) Osmotic dilators + mifepristone + misoprostol: 27.9 (5.6) Osmotic dilators + placebo + misoprostol: 27.2 (5.1) Gestational age in weeks (mean; standard deviation in parentheses): Mifepristone + misoprostol: 21.2 (1.3) Osmotic dilators + mifepristone + misoprostol: 20.9 (1.2) Osmotic dilators + placebo + misoprostol: 20.9 (1.5) Nulliparous (number; percentage in parentheses): Mifepristone + misoprostol: 4 (14.8) Osmotic dilators + mifepristone + misoprostol: 10 (37) Osmotic dilators + placebo + misoprostol: 3 (14.3)	anaesthesia, following a paracervical block of 10ml of 1% lidocaine and 4U vasopressin. **Mifepristone + misoprostol:** The day before the termination women received 200mg oral mifepristone **Osmotic dilators + mifepristone + misoprostol:** The day before the termination women had 3 to 5 osmotic dilators (Dilapan-S, 4mm) placed following a 10ml paracervical block of 1% lidocaine and 200mg oral mifepristone **Osmotic dilators + placebo + misoprostol:** The day before the termination women had 3 to 5 osmotic dilators (Dilapan-S, 4mm) placed following a 10ml paracervical block of 1% lidocaine and an oral placebo	**Outcome: Uterine perforation** Mifepristone + misoprostol: 2/27 Osmotic dilators + mifepristone + misoprostol: 1/27 Osmotic dilators + placebo + misoprostol: 0/21	outcomes; high risk for subjective outcomes Attrition: moderate risk for procedure time as 3 women were excluded from analysis due to perforation; low risk for remaining outcomes Selective reporting: moderate risk, all outcomes stated in method reported but full data was not reported for baseline cervical dilation, procedure duration, or patient acceptability or pain **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	Prior vaginal delivery (number; percentage in parentheses): Mifepristone + misoprostol: 14 (52) Osmotic dilators + mifepristone + misoprostol: 12 (44) Osmotic dilators + placebo + misoprostol: 10 (48) Prior caesarean section (number; percentage in parentheses): Mifepristone + misoprostol: 4 (15) Osmotic dilators + mifepristone + misoprostol: 1 (4) Osmotic dilators + placebo + misoprostol: 3 (14) **Inclusion criteria** Women aged at least 18 years old, fluent in English and Spanish, with a viable single pregnancy between 19^{+0} and 23^{+6} weeks' gestation eligible for outpatient surgical termination of pregnancy **Exclusion criteria** Known allergy to mifepristone and/or misoprostol			

BMI: body mass index; D&E: dilatation and evacuation; ITT: intention-to-treat; IUD: intrauterine device; mcg: micrograms; STI: sexually transmitted infection

Appendix E – Forest plots

Forest plots for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

Comparison 1. Misoprostol versus placebo or no agent

Figure 2: Incomplete abortion (400-600mcg misoprostol; 2-3 hours before termination)

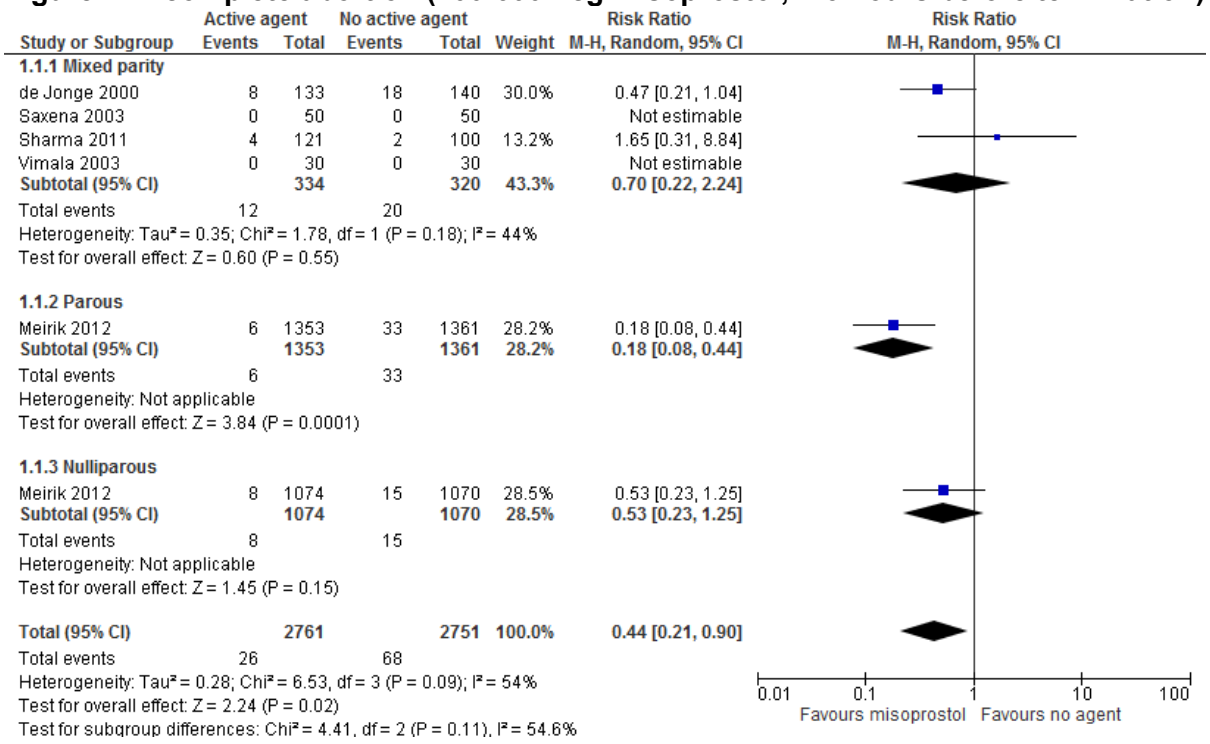


Figure 3: Cervical trauma (400-800mcg misoprostol; 1-3 hours before termination)

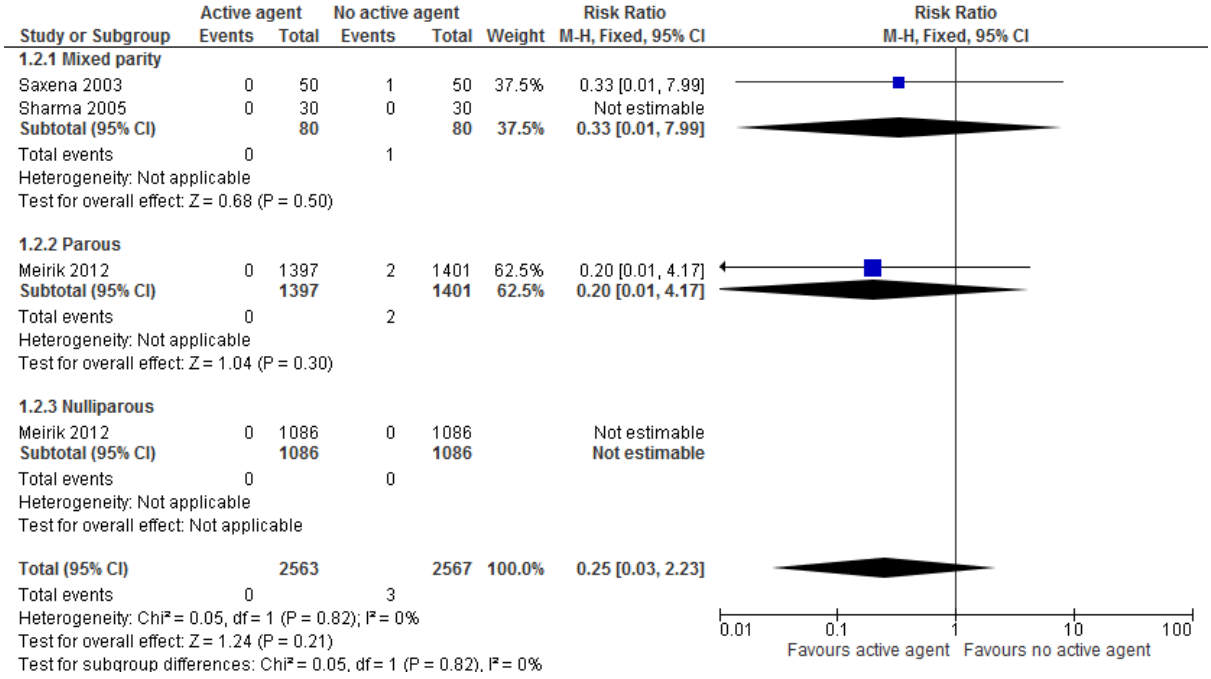


Figure 4: Uterine perforation (400-800mcg misoprostol; 1-3 hours before termination)

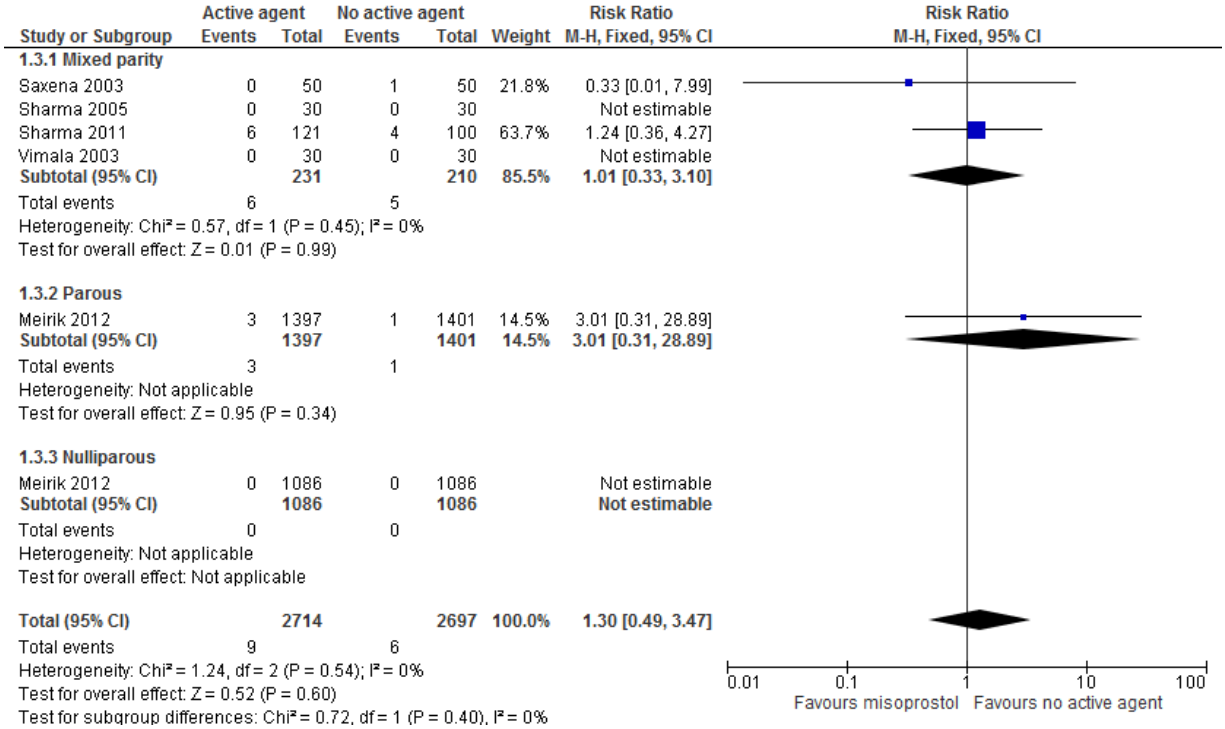


Figure 5: Cumulative force (N) required to sufficiently dilate cervix (400-800mcg misoprostol; 1-6 hours before termination)

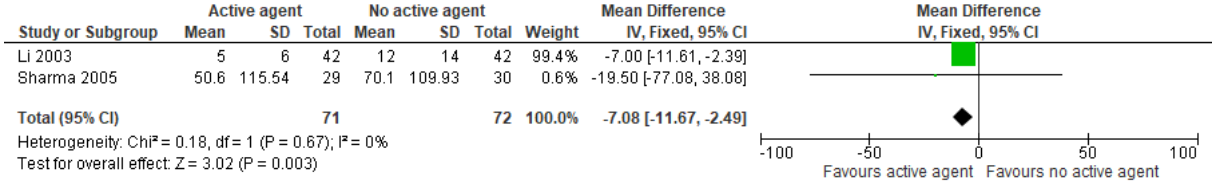


Figure 6: Pre-operative pain (400-800mcg misoprostol; 1-6 hours before termination)

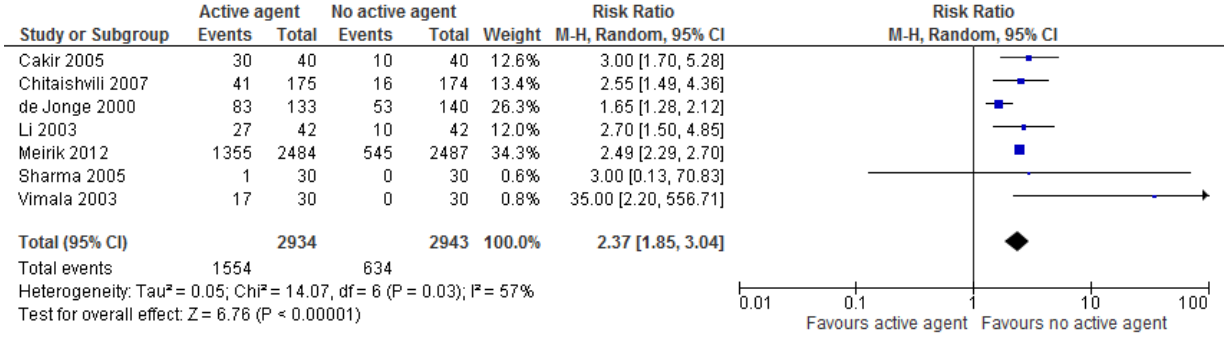
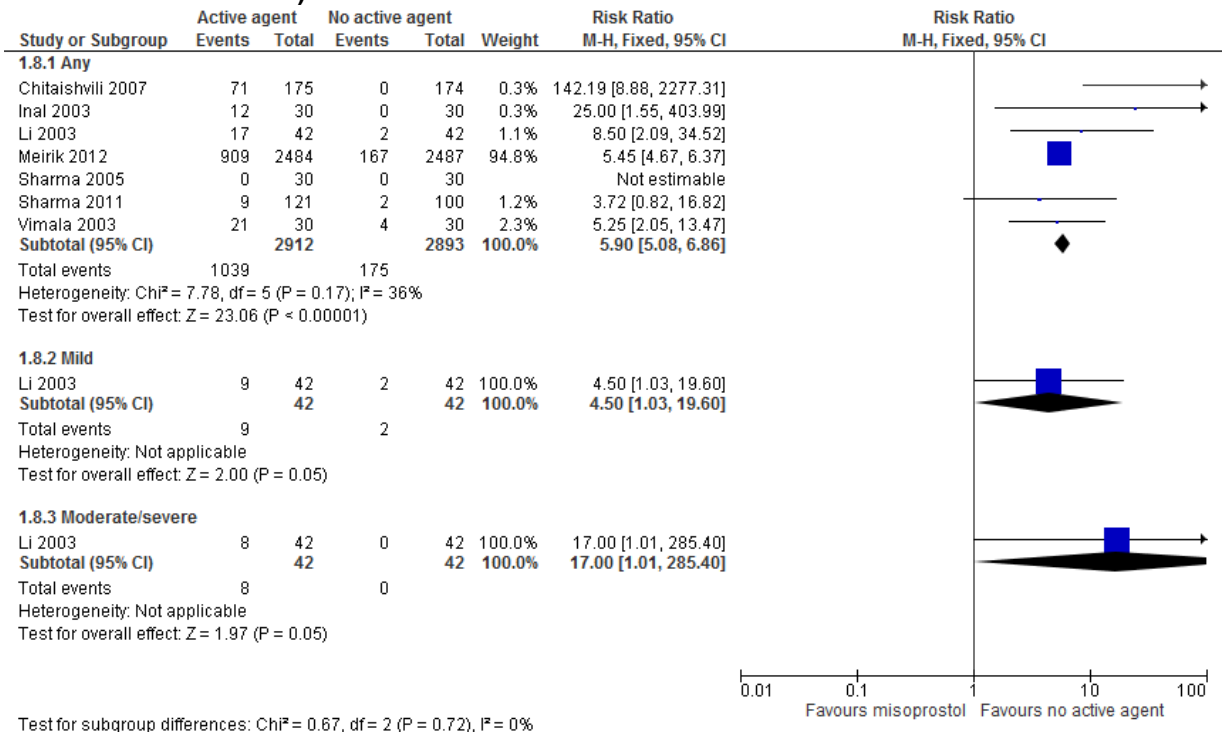


Figure 7: Pre-operative bleeding (200-800mcg misoprostol; 1-10 hours before termination)



Comparison 5. Sublingual misoprostol versus vaginal misoprostol (both 400mcg; 1-3 hours before termination)

Figure 8: Cumulative force (N) required to sufficiently dilate cervix - nulliparous

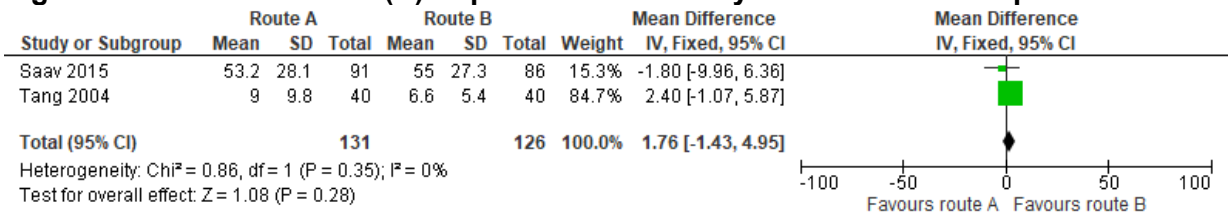


Figure 9: Pre-operative pain: any - nulliparous – not pooled due to high heterogeneity (I^2=91%)

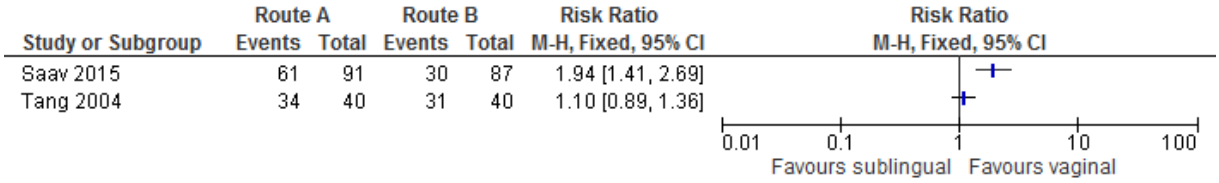


Figure 10: Pre-operative pain: any – mixed parity

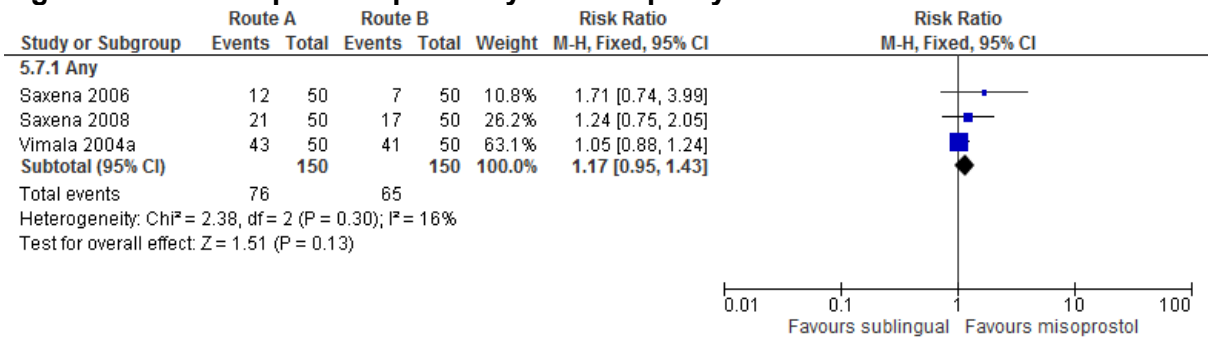


Figure 11: Pre-operative bleeding - nulliparous

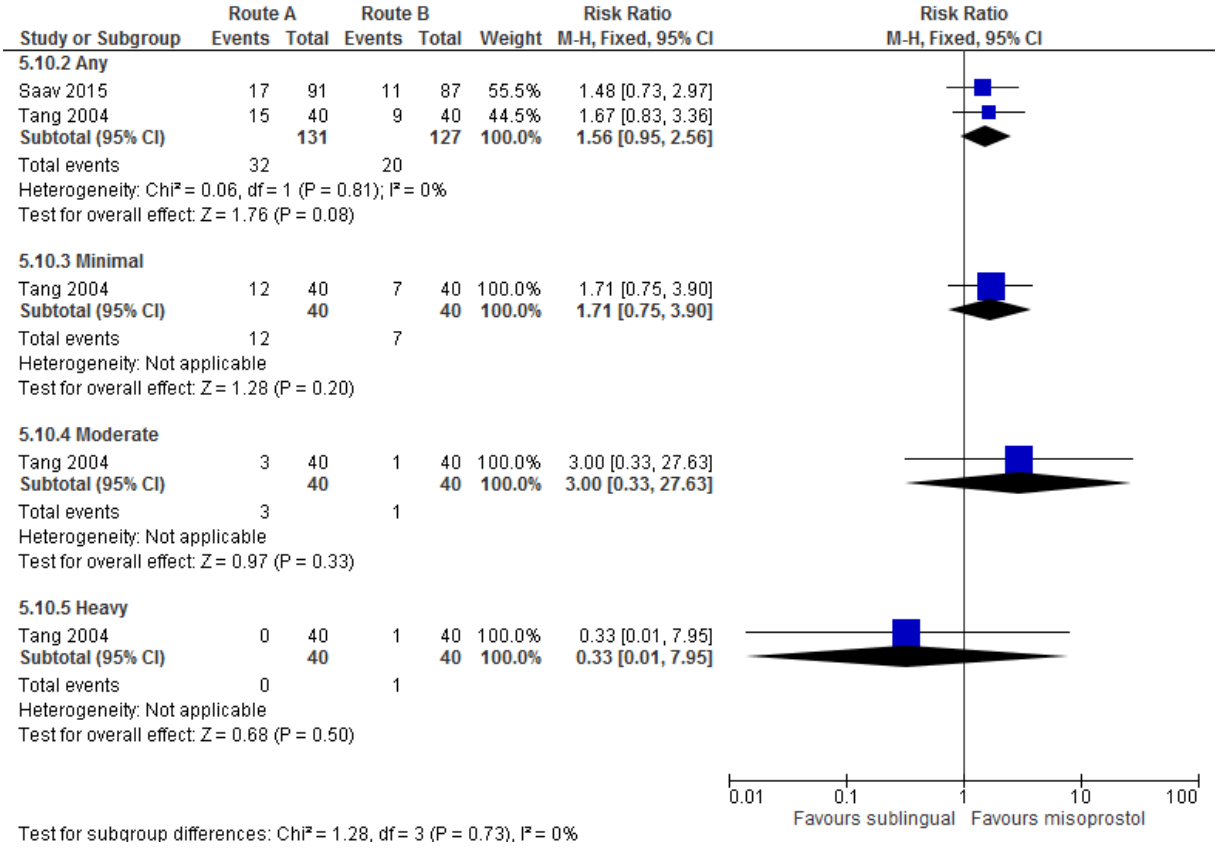
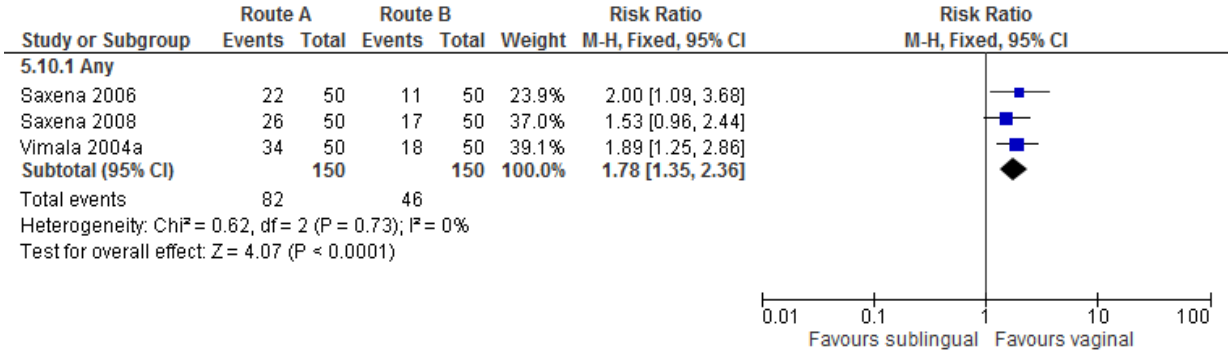


Figure 12: Pre-operative bleeding: any – mixed parity



Forest plots for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

Comparison 1. Single agent A versus single agent B

Figure 13: Baseline cervical dilation (mm) - osmotic dilators (± placebo) versus misoprostol (400-600mcg; at least 3 hours before termination) – not pooled due to high heterogeneity (I^2=93%)

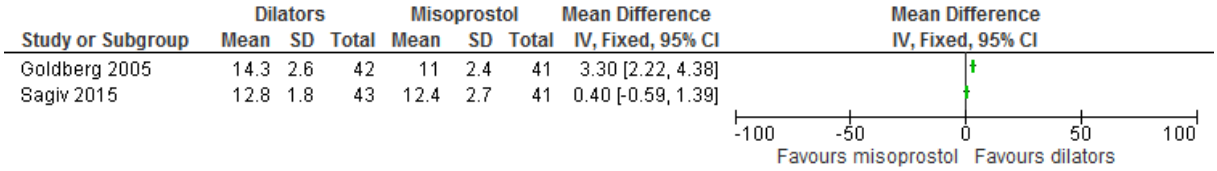


Figure 14: Uterine perforation - osmotic dilators (± placebo) versus misoprostol (400mcg; at least 3 hours before termination)

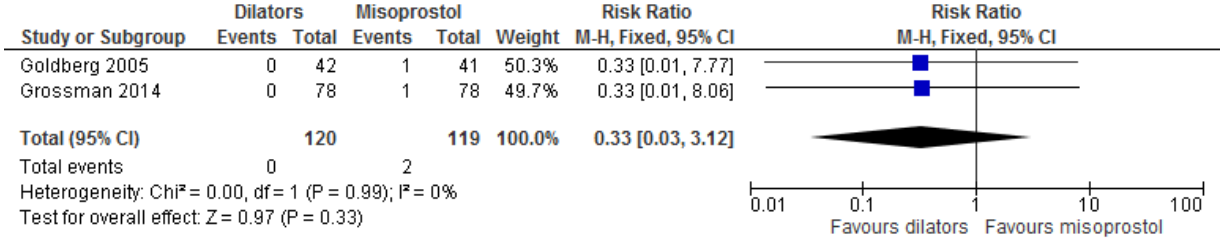
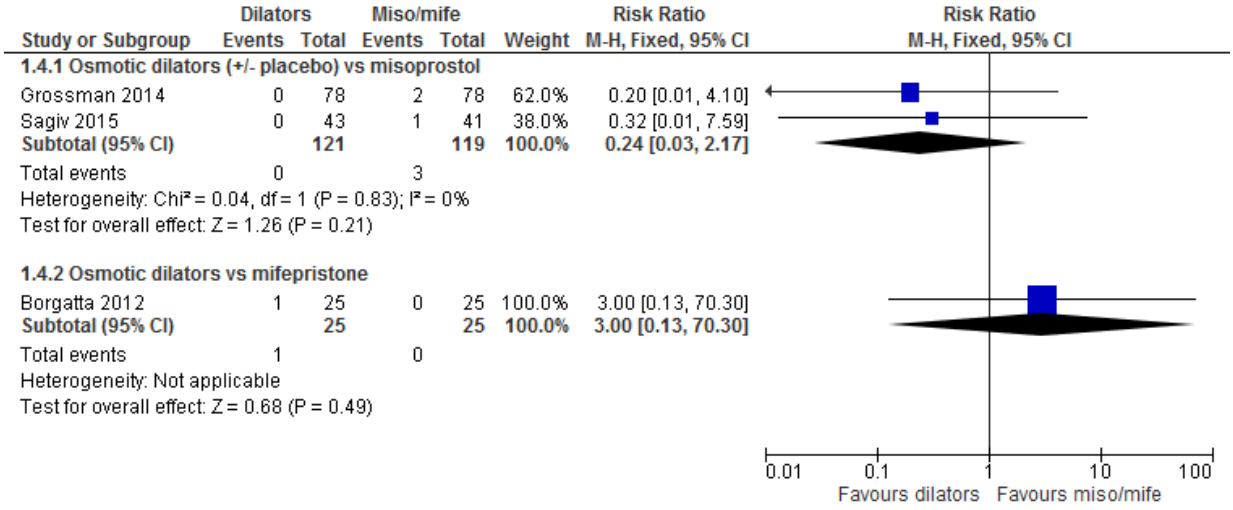


Figure 15: Pre-operative expulsion (400-600mcg misoprostol; 200mg mifepristone 20-24 hours before termination))



Comparison 2. Combination of agents versus single agent

Figure 16: Baseline cervical dilation: Osmotic dilators + buccal misoprostol (400mcg; 1-3 hours before termination) versus osmotic dilators (± placebo)

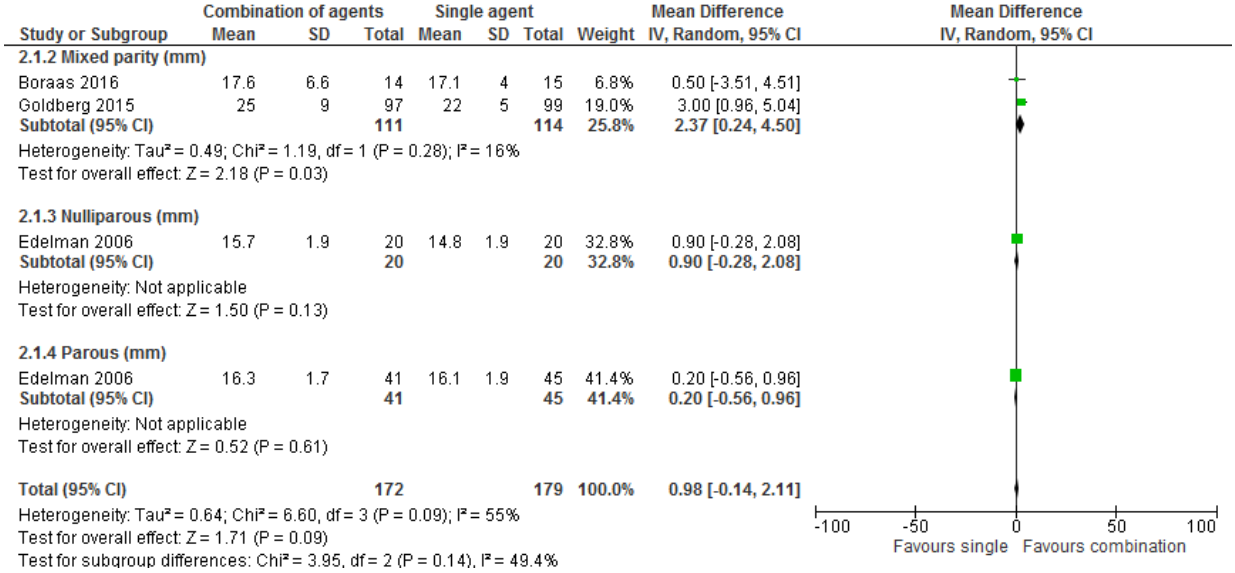


Figure 17: Baseline cervical dilation – not pooled due to high heterogeneity (I^2=96%) – (400-600mcg misoprostol 1.5-6 hours before termination; 200mg mifepristone 4-48 hours before termination)

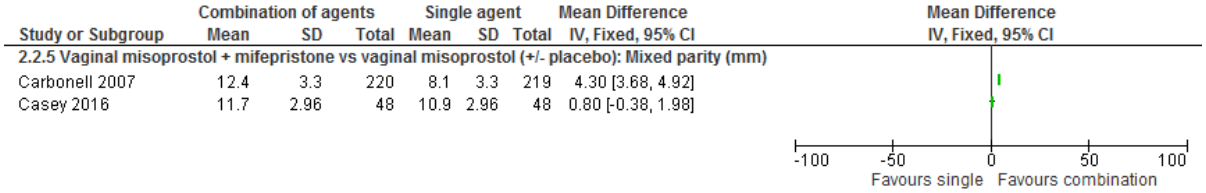


Figure 18: Cervical trauma (lacerations) - (400mcg misoprostol; 3-4 hours before termination)

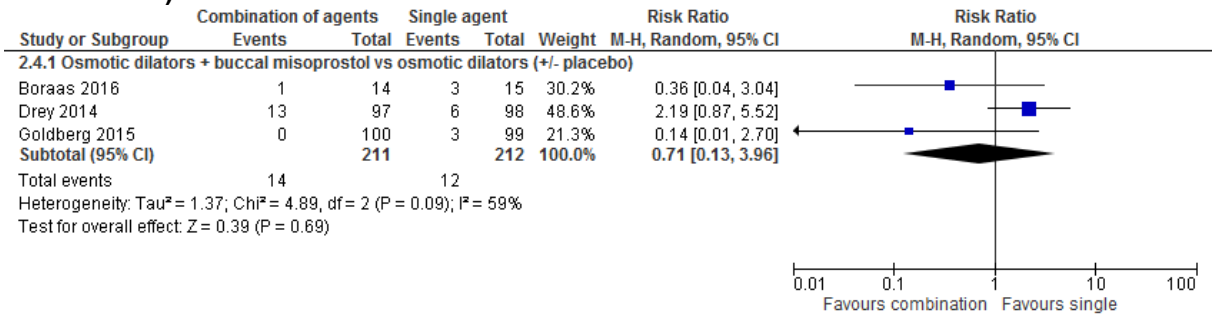


Figure 19: Uterine perforation (400mcg misoprostol 3-6 hours before termination; 200mg mifepristone 4-24 hours before termination)

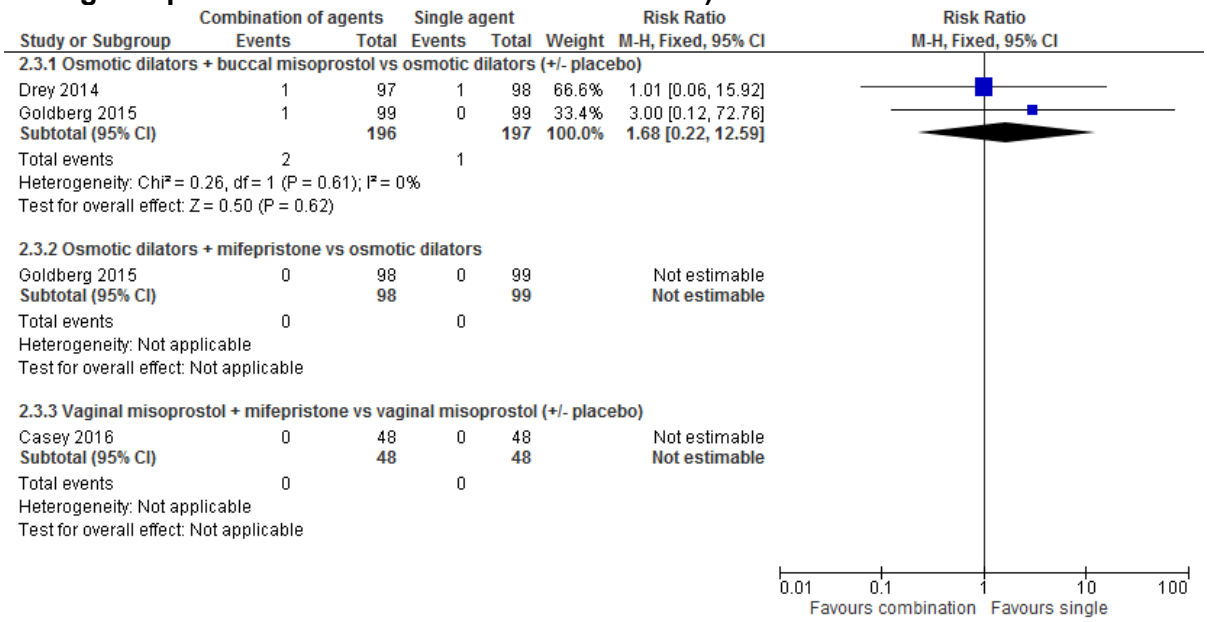


Figure 20: Pre-operative expulsion (400-600mcg misoprostol 1.5-6 hours before termination; 200mg mifepristone 4-48 hours before termination)

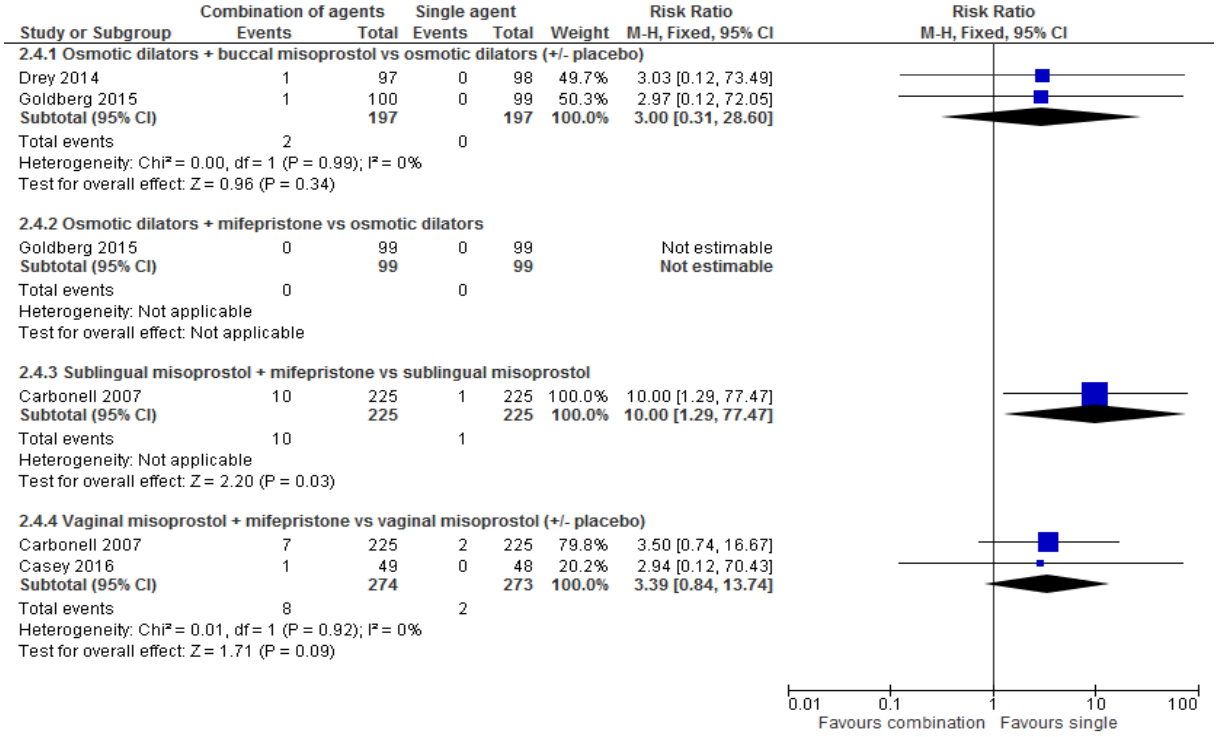


Figure 21: Ease of procedure (physician reported) - rated as (very/extremely) difficult (400mcg misoprostol 3-4 hours before termination; 200mg mifepristone 24 hours before termination)

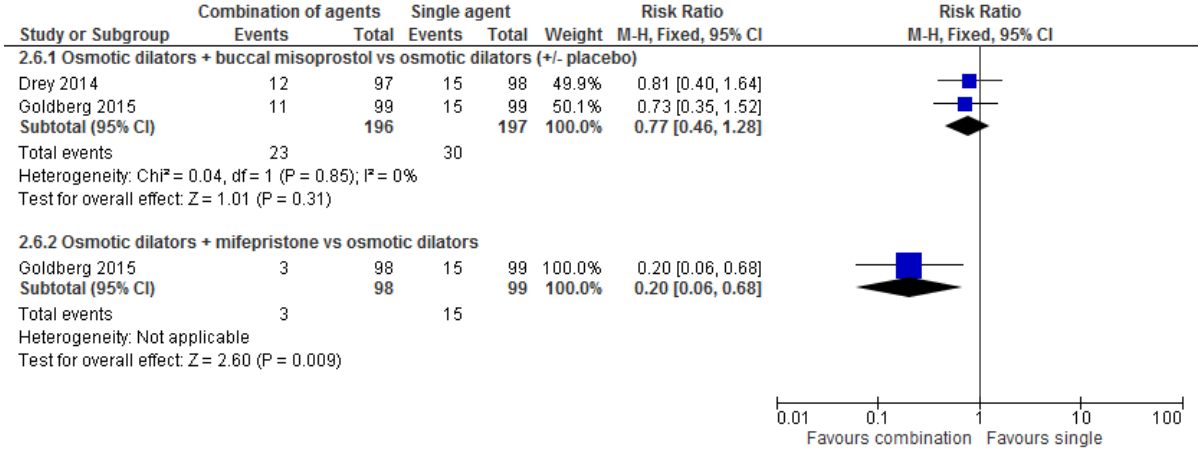


Figure 22: Patient acceptability – satisfied/very satisfied with priming (400mcg misoprostol 3 hours before termination; 200mg mifepristone 24 hours before termination)

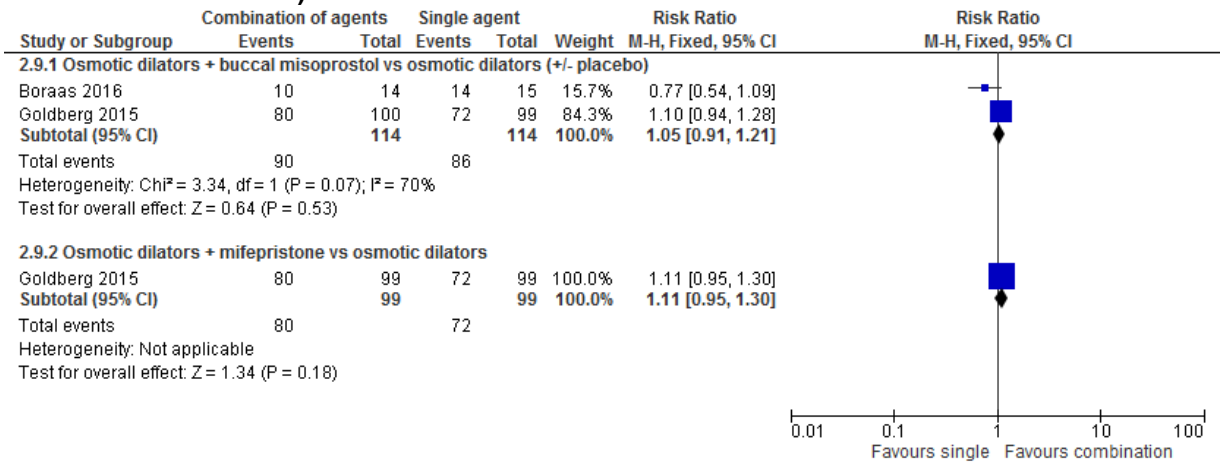


Figure 23: Patient acceptability – dissatisfied/very dissatisfied with priming (400mcg misoprostol 3 hours before termination; 200mg mifepristone 24 hours before termination)

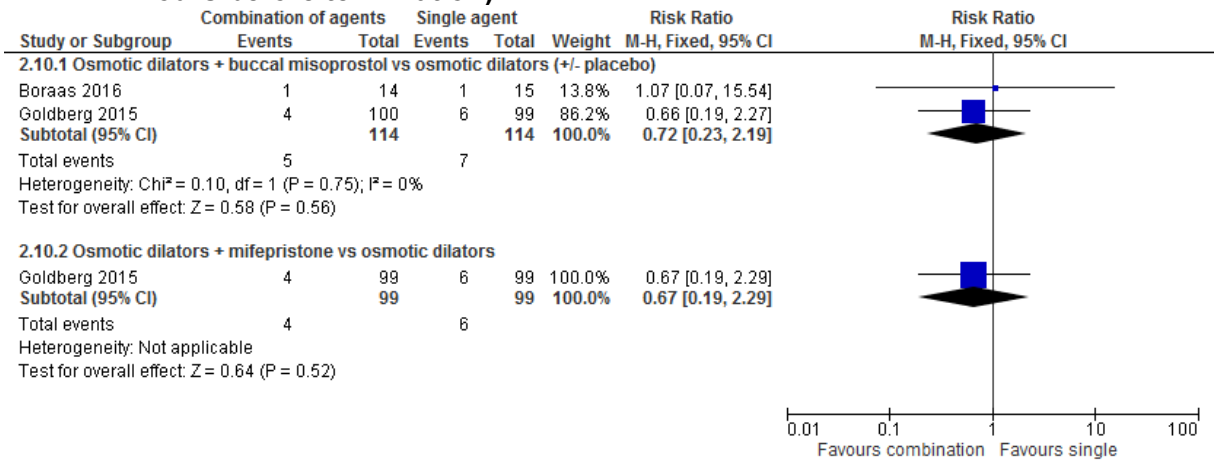


Figure 24: Duration of procedure (minutes; first instrument in to last instrument out; 400mcg misoprostol 1-4 hours before termination)

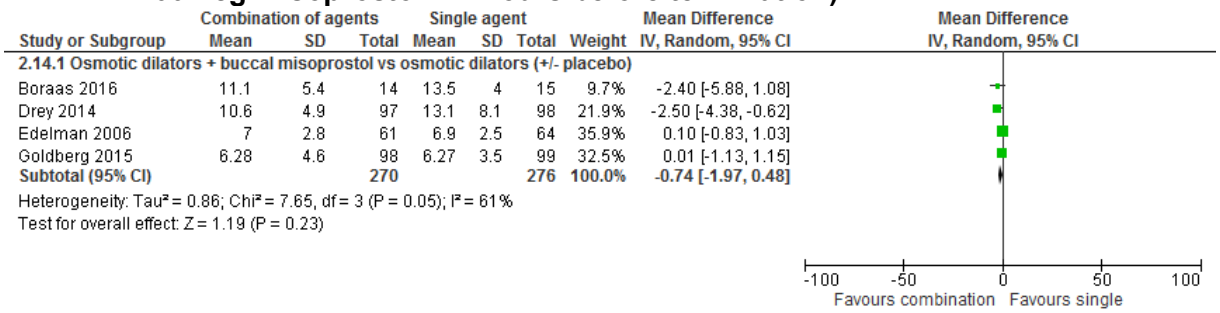
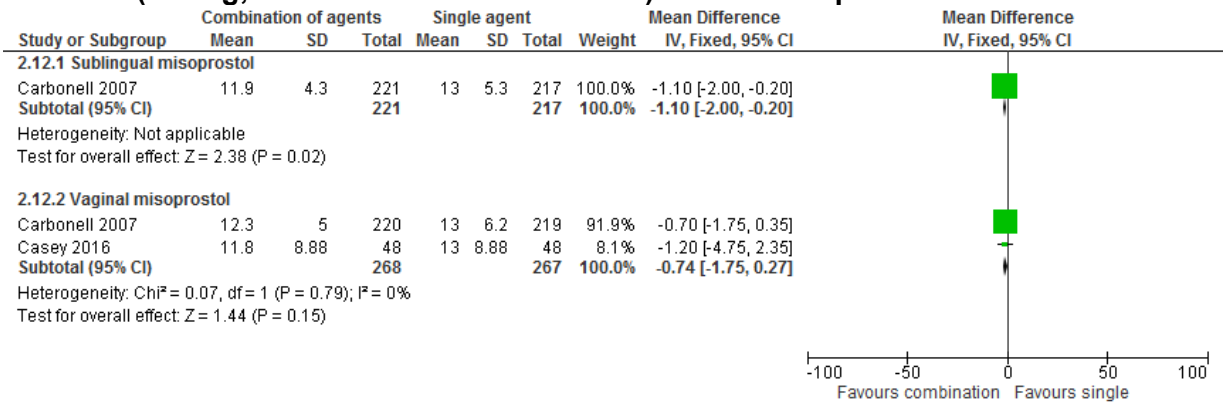


Figure 25: Duration of procedure (minutes; anaesthesia administered to speculum out) – misoprostol (600mcg; 1.5-2.5 hours before termination) + mifepristone (200mg; 48 hours before termination) versus misoprostol



Appendix F – GRADE tables

GRADE tables for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

Table 7: Clinical evidence profile: Comparison 1. Misoprostol versus no cervical priming agent (± placebo)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	No cervical priming agent (± placebo)	Relative (95% CI)	Absolute	Quality	Importance
Incomplete abortion - Mixed parity (400-600micrograms (mcg) misoprostol; 2-3 hours before termination)												
5 (de Jonge 2000; Meirik 2012; Saxena 2003; Sharma 2011; Vimala 2003)	Randomised trials	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	26/2761 (0.94%)	68/2751 (2.5%)	RR 0.44 (0.21 to 0.9)	12 fewer per 1000 (from 2 fewer to 20 fewer)	VERY LOW	CRITICAL
Incomplete abortion – Parous (400-600mcg misoprostol; 2-3 hours before termination)												
1 (Meirik 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	6/1353 (0.4%)	33/1361 (2.4%)	RR 0.18 (0.08 to 0.44)	20 fewer per 1000 (from 14 fewer to 22 fewer)	HIGH	CRITICAL
Incomplete abortion – Nulliparous (400mcg misoprostol; 3 hours before termination)												
1 (Meirik 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	8/1074 (0.7%)	15/1070 (1.4%)	RR 0.53 (0.23 to 1.25)	7 fewer per 1000 (from 11 fewer to 4 more)	MODERATE	CRITICAL
Cervical trauma - Mixed parity (400-800mcg misoprostol; 1-3 hours before termination)												

3 (Meirik 2012; Saxena 2003; Sharma 2005)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/2563 (0%)	3/2567 0.12%)	RR 0.25 (0.03 to 2.23)	8 fewer per 1000 (from 12 fewer to 87 more)	VERY LOW	CRITICAL
Cervical trauma – Parous (400mcg misoprostol; 3 hours before termination)												
1 (Meirik 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/1397 (0%)	2/1401 (0.14%)	RR 0.2 (0.01 to 4.17)	1 fewer per 1000 (from 1 fewer to 5 more)	LOW	CRITICAL
Cervical trauma – Nulliparous (400mcg misoprostol; 3 hours before termination)												
1 (Meirik 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	0/1086 (0%)	0/1086 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation - Mixed parity (400-800mcg misoprostol; 1-3 hours before termination)												
5 (Meirik 2012; Saxena 2003; Sharma 2005; Sharma 2011; Vimala 2003)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	9/2714 0.33%)	6/2697 (0.22%)	RR 1.30 (0.49 to 3.47)	1 more per 1000 (from 1 fewer to 5 more)	VERY LOW	CRITICAL
Uterine perforation – Parous (400mcg misoprostol; 3 hours before termination)												
1 (Meirik 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/1397 (0.2%)	1/1401 (0.1%)	RR 3.01 (0.31 to 28.89)	1 more per 1000 (from 0 fewer to 20 more)	LOW	CRITICAL
Uterine perforation – Nulliparous (400mcg misoprostol; 3 hours before termination)												
1 (Meirik 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	0/1086 (0%)	0/1086 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Cumulative force (N) required to sufficiently dilate cervix (400-800mcg misoprostol; 1-6 hours before termination) (Better indicated by lower values)												
2 (Li 2003;	Randomised trials	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	71	72	Not relevant	MD 7.08 lower	HIGH	IMPORTANT

Sharma 2005)		risk of bias								(11.67 to 2.49 lower)		
Pre-operative pain – Any: random effects due to heterogeneity (400-800mcg misoprostol; 1-6 hours before termination)												
7 (Cakir 2005; Chitaishvili 2007; de Jonge 2000; Li 2003; Meirik 2012; Sharma 2005; Vimala 2003)	Randomised trials	Very serious[7]	Serious[8]	No serious indirectness	No serious imprecision	None	1554/2934 (53%)	634/2943 (21.5%)	RR 2.37 (1.85 to 3.04)	295 more per 1000 (from 183 more to 439 more)	VERY LOW	IMPORTANT
Pre-operative pain - Any (unclear whether pain is pre-operative) (400mcg misoprostol; 3 hours before termination)												
1 (Sharma 2011)	Randomised trials	Serious[9]	No serious inconsistency	Serious[10]	No serious imprecision	None	9/121 (7.4%)	20/100 (20%)	RR 0.37 (0.18 to 0.78)	126 fewer per 1000 (from 44 fewer to 164 fewer)	LOW	IMPORTANT
Pre-operative pain – Mild (400mcg misoprostol; 4-6 hours before termination)												
1 (Li 2003)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	9/42 (21.4%)	10/42 (23.8%)	RR 0.9 (0.41 to 1.99)	24 fewer per 1000 (from 140 fewer to 236 more)	LOW	IMPORTANT
Pre-operative pain - Moderate/severe (400mcg misoprostol; 4-6 hours before termination)												
1 (Li 2003)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	18/42 (42.9%)	0/42 (0%)	RR 37 (2.3 to 594.63)	Not estimable	HIGH	IMPORTANT
Pre-operative expulsion (400mcg misoprostol; 3 hours before termination)												
1 (Cakir 2005)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[6]	None	0/40 (0%)	0/40 (0%)	Not estimable	Note estimable	LOW	IMPORTANT
Pre-operative bleeding – Any (200-800mcg misoprostol; 1-10 hours before termination												

7 (Chitaishvili 2007; Inal 2003; Li 2003; Meirik 2012; Sharma 2005; Sharma 2011; Vimala 2003)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1039/2912 (35.7%)	175/2893 (6%)	RR 5.9 (5.08 to 6.86)	296 more per 1000 (from 247 more to 354 more)	HIGH	IMPORTANT
Pre-operative bleeding – Mild (400mcg misoprostol; 4-6 hours before termination)												
1 (Li 2003)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	9/42 (21.4%)	2/42 (4.8%)	RR 4.5 (1.03 to 19.6)	167 more per 1000 (from 1 more to 886 more)	MODERATE	IMPORTANT
Pre-operative bleeding - Moderate/severe (400mcg misoprostol; 4-6 hours before termination)												
1 (Li 2003)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	8/42 (19%)	0/42 (0%)	RR 17 (1.01 to 285.4)	Not estimable	MODERATE	IMPORTANT
Pre-operative bleeding (in ml) (400mcg misoprostol; 3 hours before termination)												
1 (Cakir 2005)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	40	40	Not relevant	MD 2.9 higher (2.61 to 3.19 higher)	MODERATE	IMPORTANT

CI: confidence interval; mcg: micrograms; MD: mean difference; MID: minimally important difference; RR: relative risk

[1] The quality of evidence was downgraded 1 level as there was insufficient information provided regarding randomisation method and allocation concealment for the study with the largest weight in the analysis

[2] The quality of evidence was downgraded 1 level as there were high rates of unexplained heterogeneity (54%)

[3] The quality of evidence was downgraded by 1 as the 95% confidence interval crossed 1 MID

[4] The quality of evidence was downgraded 1 level as there was insufficient information provided regarding allocation concealment

[5] The quality of evidence was downgraded by 2 as the 95% confidence interval crossed 2 MIDs

[6] Not sufficiently powered to detect this rare outcome; no events of interest

[7] The quality of evidence was downgraded 2 levels as there was insufficient information provided regarding randomisation method and allocation concealment in 2 of the included trials; further this a subjective, patient reported outcome and there was no blinding in 1 of the included trials

[8] *The quality of evidence was downgraded 1 level as there were high rates of unexplained heterogeneity (64%) as there was no data for subgroups of interest*
[9] *The quality of evidence was downgraded 1 level as this is a subjective patient reported outcome and insufficient information was provided regarding blinding to treatment allocation*
[10] *The quality of evidence was downgraded 1 level as it was unclear if this outcome referred to pre-operative pain; reported as 'No. of women having abdominal pain'*

Table 8: Clinical evidence profile: Comparison 2. Mifepristone versus misoprostol

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mifepristone (200mg; 24 hours before termination)**	**Misoprostol (800micrograms (mcg); 2-4 hours before termination)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Cumulative force (N) required to sufficiently dilate cervix (Better indicated by lower values)												
1 (Ashok 2000)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	30	30	Not relevant	MD 2.3 lower (15.41 lower to 10.81 higher)	LOW	IMPORTANT
Pre-operative pain												
1 (Ashok 2000)	Randomised trials	Very serious[3]	Serious[2]	No serious indirectness	Serious[2]	None	37/60 (61.7%)	20/29 (69%)	RR 0.89 (0.65 to 1.23)	76 fewer per 1000 (from 241 fewer to 159 more)	VERY LOW	IMPORTANT
Pre-operative bleeding												
1 (Ashok 2000)	Randomised trials	Very serious[1, 3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	8/60 (13.3%)	3/29 (10.3%)	RR 1.29 (0.37 to 4.5)	30 more per 1000 (from 65 fewer to 362 more)	VERY LOW	IMPORTANT

CI: confidence interval; mcg: micrograms; MD: mean difference; MID: minimally important difference; RR: relative risk
[1] *The quality of evidence was downgraded 1 level as insufficient information was reported regarding random sequence generation*
[2] *The quality of evidence was downgraded by 1 as the 95% confidence interval crosses 1 MID*
[3] *The quality of evidence was downgraded 2 levels as insufficient information was reported regarding random sequence generation and this is a subjective patient reported outcome and patients were not blind to treatment allocation*
[4] *The quality of evidence was downgraded by 2 as the 95% confidence interval crosses 2 MIDs*

Table 9: Clinical evidence profile: Comparison 3. Sublingual misoprostol 400mcg versus sublingual misoprostol 200mcg (both given 2-3 hours before termination)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	400micrograms (mcg)	200mcg	Relative (95% CI)	Absolute		
Incomplete abortion												
1 (Vimala 2004b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/30 (0%)	0/60 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation												
1 (Vimala 2004b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/30 (0%)	0/60 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Pre-operative pain												
1 (Vimala 2004b)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	17/30 (56.7%)	28/60 (46.7%)	RR 1.21 (0.8 to 1.84)	98 more per 1000 (from 93 fewer to 392 more)	LOW	IMPORTANT
Pre-operative expulsion												
1 (Vimala 2004b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/30 (0%)	0/60 (0%)	Not estimable	Not estimable	MODERATE	IMPORTANT
Pre-operative bleeding												
1 (Vimala 2004b)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	20/30 (66.7%)	36/60 (60%)	RR 1.11 (0.8 to 1.54)	66 more per 1000 (from 120 fewer to 324 more)	LOW	IMPORTANT

CI: confidence interval; mcg: micrograms; MD: mean difference; MID: minimally important difference; RR: relative risk

[1] Not sufficiently powered to detect this rare outcome; no events of interest

[2] The quality of evidence was downgraded 1 level as this is a subjective patient reported outcome and women were not blind to treatment allocation

[3] The quality of evidence was downgraded by 1 level as the 95% confidence interval crosses 1 MID

Table 10: Clinical evidence profile: Comparison 4. Cervical priming agent A interval A versus cervical priming agent A interval B

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interval A	Interval B	Relative (95% CI)	Absolute	Quality	Importance
Incomplete abortion - Sublingual misoprostol (400micrograms (mcg)): 2hr interval versus 3hr interval												
1 (Vimala 2004b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/30 (0%)	0/30 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Cervical trauma - Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/45 (0%)	0/46 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Cervical trauma - Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/43 (0%)	0/44 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation - Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/45 (0%)	0/46 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation - Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/43 (0%)	0/44 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation - Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval												
1 (Vimala 2004b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/30 (0%)	0/30 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Cumulative force (N) required to sufficiently dilate cervix – Mifepristone (200mg): 24hr interval versus 48hr interval (Better indicated by lower values)												
1 (Ashok 2000)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	30	30	Not relevant	MD 14.3 higher (2.13 to	LOW	IMPORTANT

										26.47 higher)		
Cumulative force (N) required to sufficiently dilate cervix - Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous (Better indicated by lower values)												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	45	46	Not relevant	MD 2.5 lower (14.05 lower to 9.05 higher)	HIGH	IMPORTANT
Cumulative force (N) required to sufficiently dilate cervix - Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous (Better indicated by lower values)												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	43	44	Not relevant	MD 17.5 higher (5.88 to 29.12 higher)	MODERATE	IMPORTANT
Pre-operative pain – Mifepristone (200mg): 24hr interval versus 48hr interval												
1 (Ashok 2000)	Randomised trials	Very serious[4]	No serious inconsistency	No serious indirectness	Serious[3]	None	16/30 (53.3%)	21/30 (70%)	RR 0.76 (0.51 to 1.15)	168 fewer per 1000 (from 343 fewer to 105 more)	VERY LOW	IMPORTANT
Pre-operative pain - Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Very serious[6]	None	30/45 (66.7%)	31/46 (67.4%)	RR 0.99 (0.74 to 1.32)	7 fewer per 1000 (from 175 fewer to 216 more)	VERY LOW	IMPORTANT
Pre-operative pain - Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	6/43 (14%)	24/44 (54.5%)	RR 0.26 (0.12 to 0.56)	404 fewer per 1000 (from 240 fewer to 480 fewer)	MODERATE	IMPORTANT
Pre-operative pain - Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval												
1 (Vimala 2004b)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Very serious[4]	None	17/30 (56.7%)	20/30 (66.7%)	RR 0.85 (0.57 to 1.27)	100 fewer per 1000 (from 287 fewer to 180 more)	VERY LOW	IMPORTANT
Pre-operative expulsion - Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												

1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/45 (0%)	0/46 (0%)	Not estimable	Not estimable	MODERATE	IMPORTANT
Pre-operative expulsion - Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/43 (0%)	0/44 (0%)	Not estimable	Not estimable	MODERATE	IMPORTANT
Pre-operative expulsion - Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval												
1 (Vimala 2004b)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/30 (0%)	0/30 (0%)	Not estimable	Not estimable	MODERATE	IMPORTANT
Pre-operative bleeding – Mifepristone (200mg): 24hr interval versus 48hr interval												
1 (Ashok 2000)	Randomised trials	Very serious[4]	No serious inconsistency	No serious indirectness	Very serious[6]	None	2/30 (6.7%)	6/30 (20%)	RR 0.33 (0.07 to 1.52)	134 fewer per 1000 (from 186 fewer to 104 more)	VERY LOW	IMPORTANT
Pre-operative bleeding - Sublingual misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2/45 (4.4%)	15/46 (32.6%)	RR 0.14 (0.03 to 0.56)	280 fewer per 1000 (from 143 fewer to 316 fewer)	MODERATE	IMPORTANT
Pre-operative bleeding - Vaginal misoprostol (400mcg): 1hr interval versus 3hr interval - nulliparous												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	None	3/43 (7%)	8/44 (18.2%)	RR 0.38 (0.11 to 1.35)	113 fewer per 1000 (from 162 fewer to 64 more)	LOW	IMPORTANT
Pre-operative bleeding - Sublingual misoprostol (400mcg): 2hr interval versus 3hr interval												
1 (Vimala 2004b)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Serious[3]	None	20/30 (66.7%)	23/30 (76.7%)	RR 0.87 (0.63 to 1.2)	100 fewer per 1000 (from 284 fewer to 153 more)	LOW	IMPORTANT

CI: confidence interval; hr: hour; mcg: micrograms; MD: mean difference; MID: minimally important difference; RR: relative risk

[1] Not sufficiently powered to detect this rare outcome; no events of interest

[2] The quality of evidence was downgraded 1 level as insufficient information was provided regarding random sequence generation

[3] *The quality of evidence was downgraded by 1 as the 95% confidence interval crosses 1 MID*
[4] *The quality of evidence was downgraded 2 levels as insufficient information was provided regarding random sequence generation and this is a subjective patient reported outcome and women were not blind to treatment allocation*
[5] *The quality of evidence was downgraded 1 level as this is as subjective patient reported outcome and women were not blind to treatment allocation*
[6] *The quality of evidence was downgraded by 2 as the 95% confidence interval crosses 2 MIDs*

Table 11: Clinical evidence profile: Comparison 5. Sublingual misoprostol versus vaginal misoprostol (both 400mcg; 1-3 hours before termination)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sublingual misoprostol**	**Vaginal misoprostol**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Incomplete abortion												
1 (Vimala 2004a)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	0/50 (0%)	0/50 (0%)	Not estimable	Not estimable	LOW	CRITICAL
Cervical trauma – mixed parity												
1 (Carbonell Esteve 2006)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	0/626 (0%)	0/632 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Cervical trauma – nulliparous												
1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	0/91 (0%)	0/87 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation – mixed parity												
2 (Carbonell Esteve 2006; Vimala 2004a)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	0/676 (0%)	0/682 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation – nulliparous												

1 (Saav 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	0/91 (0%)	0/87 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Cumulative force (N) required to sufficiently dilate cervix – nulliparous (Better indicated by lower values)												
2 (Saav 2015; Tang 2004)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	131	126	Not relevant	MD 1.76 higher (1.43 lower to 4.95 higher)	MODERATE	IMPORTANT
Ease of cervical dilation - No further dilation needed												
1 (Carbonbell Esteve 2006)	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	224/626 (35.8%)	184/632 (29.1%)	RR 1.23 (1.05 to 1.44)	67 more per 1000 (from 15 more to 128 more)	LOW	IMPORTANT
Ease of cervical dilation – Easy												
1 (Carbonbell Esteve 2006)	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	299/626 (47.8%)	339/632 (53.6%)	RR 0.89 (0.8 to 0.99)	59 fewer per 1000 (from 5 fewer to 107 fewer)	MODERATE	IMPORTANT
Ease of cervical dilation – Normal												
1 (Carbonbell Esteve 2006)	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	86/626 (13.7%)	83/632 (13.1%)	RR 1.05 (0.79 to 1.38)	7 more per 1000 (from 28 fewer to 50 more)	VERY LOW	IMPORTANT
Ease of cervical dilation – Difficult												
1 (Carbonbell Esteve 2006)	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	17/626 (2.7%)	26/632 (4.1%)	RR 0.66 (0.36 to 1.2)	14 fewer per 1000 (from 26 fewer to 8 more)	LOW	IMPORTANT
Pre-operative pain – Any – nulliparous: not pooled due to heterogeneity												
2 (Saav 2015; Tang 2004)	Randomised trials	Very serious[6]	Very serious[7]	No serious indirectness	Very serious[5]	None	95/131 (72/5%)	61/127 (48%)	Not pooled[7]: Saav 2015: RR 1.94	Not pooled[7]	VERY LOW	

									(1.41 to 2.69) Tang 2004: RR 1.10 (0.89 to 1.36)			
Pre-operative pain – Any – mixed parity												
3 (Saxena 2006; Saxena 2008; Vimala 2004a)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[4]	None	76/150 (50.7%)	65/150 (43.3%)	RR 1.17 (0.95 to 1.43)	74 more per 1000 (from 22 fewer to 186 more)	VERY LOW	IMPORTANT
Pre-operative pain – Mild - nulliparous												
1 (Tang 2004)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[4]	None	22/40 (55%)	17/40 (42.5%)	RR 1.29 (0.82 to 2.04)	123 more per 1000 (from 77 fewer to 442 more)	VERY LOW	IMPORTANT
Pre-operative pain – Moderate - nulliparous												
1 (Tang 2004)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	11/40 (27.5%)	9/40 (22.5%)	RR 1.22 (0.57 to 2.62)	50 more per 1000 (from 97 fewer to 364 more)	VERY LOW	IMPORTANT
Pre-operative pain – Severe - nulliparous												
1 (Tang 2004)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/40 (2.5%)	5/40 (12.5%)	RR 0.2 (0.02 to 1.64)	100 fewer per 1000 (from 123 fewer to 80 more)	VERY LOW	IMPORTANT
Pre-operative expulsion – mixed parity												
2 (Saxena 2006; Saxena 2008)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	0/100 (0%)	0/100 (0%)	Not estimable	Not estimable	LOW	IMPORTANT
Pre-operative expulsion - nulliparous												

2 (Saav 2015; Tang 2004)	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	0/131 (0%)	0/127 (0%)	Not estimable	Not estimable	LOW	IMPORTANT
Pre-operative bleeding – Any – mixed parity												
3 (Saxena 2006; Saxena 2008; Vimala 2004a)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	82/150 (54.7%)	46/150 (30.7%)	RR 1.78 (1.35 to 2.36)	239 more per 1000 (from 107 more to 417 more)	LOW	IMPORTANT
Pre-operative bleeding – Any - nulliparous												
2 (Saav 2015; Tang 2004)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[4]	None	32/131 (24.4%)	20/127 (15.7%)	RR 1.56 (0.95 to 2.56)	88 more per 1000 (from 8 fewer to 246 more)	LOW	IMPORTANT
Pre-operative bleeding – Minimal - nulliparous												
1 (Tang 2004)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	12/40 (30%)	7/40 (17.5%)	RR 1.71 (0.75 to 3.9)	124 more per 1000 (from 44 fewer to 507 more)	VERY LOW	IMPORTANT
Pre-operative bleeding – Moderate - nulliparous												
1 (Tang 2004)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/40 (7.5%)	1/40 (2.5%)	RR 3 (0.33 to 27.63)	50 more per 1000 (from 17 fewer to 666 more)	VERY LOW	IMPORTANT
Pre-operative bleeding – Heavy - nulliparous												
1 (Tang 2004)	Randomised trials	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/40 (0%)	1/40 (2.5%)	RR 0.33 (0.01 to 7.95)	17 fewer per 1000 (from 25 fewer to 174 more)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: relative risk

[1] The quality of evidence was downgraded 1 level as insufficient information was reported regarding allocation concealment

[2] Not sufficiently powered to detect this rare outcome; no events of interest

[3] The quality of evidence was downgraded 1 level as this is a subjective physician reported outcome and physicians were not blind to treatment allocation

[4] The quality of evidence was downgraded by 1 as the 95% confidence interval crosses 1 MID

[5] *The quality of evidence was downgraded by 2 as the 95% confidence interval crosses 2 MIDs*
[6] *The quality of evidence was downgraded 2 levels as this is a subjective patient reported outcome and women were not blind to treatment allocation and insufficient information was provided about allocation concealment*
[7] *The quality of evidence was downgraded 2 levels as there were high rates of unexplained heterogeneity (I squared 91%) as data was not reported for subgroups of interest*

GRADE tables for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

Table 12: Clinical evidence profile: Comparison 1. Single agent A versus single agent B

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single agent A**	**Single agent B**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Baseline cervical dilation - mm - Osmotic dilators (± placebo) versus misoprostol (400-600micrograms (mcg); at least 3 hours before termination) (Better indicated by higher values)												
2 (Goldberg 2005; Sagiv 2015)	Randomised trials	No serious risk of bias	Very Serious[1]	Serious[2]	No serious imprecision	None	85	82	Not applicable	Not Pooled[1]: Goldberg 2005: MD 3.30 higher (from 2.22 higher to 4.38 higher) Sagiv 2015: MD 0.40 higher (from 0.59 lower to 1.39 higher)	VERY LOW	CRITICAL
Baseline cervical dilation (14mm cannula passed without additional dilation) - Osmotic dilators versus mifepristone (200mg; 20-24 hours before termination)												
1 (Borgatta 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	18/24 (75%)	1/25 (4%)	RR 18.75 (2.71 to 129.72)	710 more per 1000 (from 68 more to 1000 more)	HIGH	CRITICAL

Cervical trauma (suspected) - Osmotic dilators (± placebo) versus misoprostol (400mcg; 3-4 hours before termination)												
1 (Goldberg (2005)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	0/42 (0%)	2/41 (4.9%)	RR 0.20 (0.01 to 3.95)	39 fewer per 1000 (from 48 fewer to 144 more)	VERY LOW	CRITICAL
Uterine perforation (suspected) - Osmotic dilators (± placebo) versus misoprostol (400mcg; at least 3 hours before termination)												
2 (Goldberg 2005; Grossman 2014)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	0/120 (0%)	2/119 (1.7%)	RR 0.33 (0.03 to 3.12)	11 fewer per 1000 (from 16 fewer to 36 more)	VERY LOW	CRITICAL
Pre-operative expulsion - Osmotic dilators (± placebo) versus misoprostol (400-600mcg)												
2 (Grossman 2014; Sagiv 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	0/121 (0%)	3/119 (2.5%)	RR 0.24 (0.03 to 2.17)	19 fewer per 1000 (from 24 fewer to 29 more)	VERY LOW	IMPORTANT
Pre-operative expulsion - Osmotic dilators versus mifepristone (200mg; 20-24 hours before termination)												
1 (Borgatta 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	Not estimable	LOW	IMPORTANT
Ease of procedure (physician reported) - rated as not difficult - Osmotic dilators (± placebo) versus misoprostol (400mcg; 3-4 hours before termination)												
1 (Goldberg 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[4]	None	29/42 (69%)	15/41 (36.6%)	RR 1.89 (1.2 to 2.96)	326 more per 1000 (from 73 more to 717 more)	LOW	IMPORTANT
Ease of procedure (physician reported) - rated as not difficult - Osmotic dilators versus mifepristone (200mg; 20-24 hours before termination)												
1 (Borgatta 2012)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Very serious[3]	None	11/24 (45.8%)	9/25 (36%)	RR 1.27 (0.65 to 2.51)	97 more per 1000 (from 126 fewer to 544 more)	VERY LOW	IMPORTANT
Ease of procedure (physician reported) - rated as mildly difficult - Osmotic dilators (± placebo) versus misoprostol (400mcg; 3-4 hours before termination)												
1 (Goldberg 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	10/42 (23.8%)	15/41 (36.6%)	RR 0.65 (0.33 to 1.28)	128 fewer per 1000 (from 245 fewer to 102 more)	VERY LOW	IMPORTANT

Ease of procedure (physician reported) - rated as difficult - Osmotic dilators versus mifepristone (200mg; 20-24 hours before termination)												
1 (Borgatta 2012)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[3]	None	2/24 (8.3%)	6/25 (24%)	RR 0.35 (0.08 to 1.55)	156 fewer per 1000 (from 221 fewer to 132 more)	VERY LOW	IMPORTANT
Ease of procedure (physician reported) - rated as moderately/markedly difficult - Osmotic dilators (± placebo) versus misoprostol (400mcg; 3-4 hours before termination)												
1 (Goldberg 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	2/42 (4.8%)	11/41 (26.8%)	RR 0.18 (0.04 to 0.75)	220 fewer per 1000 (from 67 fewer to 258 fewer)	MODERATE	IMPORTANT
Patient acceptability - would choose same method again - Osmotic dilators (± placebo) versus misoprostol (400mcg; 3-4 hours before termination)												
1 (Goldberg 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[4]	None	26/42 (61.9%)	38/41 (92.7%)	RR 0.67 (0.52 to 0.86)	306 fewer per 1000 (from 130 fewer to 445 fewer)	LOW	IMPORTANT
Patient acceptability - would choose same method again - Osmotic dilators versus mifepristone (200mg; 20-24 hours before termination)												
1 (Borgatta 2012)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	7/24 (29.2%)	24/25 (96%)	RR 0.3 (0.16 to 0.57)	672 fewer per 1000 (from 413 fewer to 806 fewer)	MODERATE	IMPORTANT
Patient acceptability - would prefer 1-day misoprostol to 2-day dilators - Osmotic dilators (± placebo) versus misoprostol (400mcg; 3-4 hours before termination)												
1 (Goldberg 2005)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[4]	None	32/42 (76.2%)	36/41 (87.8%)	RR 0.87 (0.71 to 1.06)	114 fewer per 1000 (from 255 fewer to 53 more)	LOW	IMPORTANT
Duration of procedure (minutes; speculum in to speculum out) - Osmotic dilators versus mifepristone (200mg; 20-24 hours before termination): Mixed parity												
1 (Borgatta 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	24	25	Not applicable	MD 1.87 lower (4.39 lower to 0.65 higher)	MODERATE	IMPORTANT
Duration of procedure (minutes; speculum in to speculum out) - Osmotic dilators (± placebo) versus misoprostol (400mcg): Nulliparous												
1 (Grossman 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[4]	None	23	17	Not applicable	MD 0.2 lower (3.27 lower to	LOW	IMPORTANT

										2.87 higher)		
Duration of procedure (minutes; speculum in to speculum out) - Osmotic dilators (± placebo) versus misoprostol (400mcg): Parous												
1 (Grossman 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	55	61	Not applicable	MD 0.5 higher (1.76 lower to 2.76 higher)	MODERATE	IMPORTANT
Duration of procedure (minutes; beginning of suction to speculum out) - Osmotic dilators versus mifepristone (200mg; 20-24 hours before termination)												
1 (Borgatta 2012)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	24	25	Not applicable	MD 0.2 lower (1.72 lower to 1.32 higher)	HIGH	IMPORTANT

CI: confidence interval; mcg: micrograms; MD: mean difference; MID: minimally important difference; RR: relative risk
[1] The quality of evidence was downgraded 2 levels as there were high rates of unexplained heterogeneity (93%) as there was no data for subgroups of interest
[2] The quality of evidence was downgraded 1 level as study includes women with gestational age from 1 week lower than population of interest for this question
[3] The quality of evidence was downgraded by 1 as the 95% confidence interval crossed 1 MID
[4] The quality of evidence was downgraded by 2 as the 95% confidence interval crosses 2 MIDs
[5] The quality of evidence was downgraded 1 level due to subjective nature of this outcome and lack of blinding

Table 13: Clinical evidence profile: Comparison 2. Combination of agents versus single agent

Quality assessment							**No of patients**		**Effect**			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination of agents**	**Single agent**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Baseline cervical dilation - Osmotic dilators + buccal misoprostol (400micrograms (mcg); 1-3 hours before termination) versus osmotic dilators (± placebo): Mixed parity (mm) (Better indicated by higher values)												
3 (Boraas 2016; Eselman 2006; Goldberg 2015)	Randomised trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	172	179	Not applicable	MD 0.98 higher (0.14 lower to 2.11 higher)	MODERATE	CRITICAL
Baseline cervical dilation - Osmotic dilators + buccal misoprostol (400mcg; 1-3 hours before termination) versus osmotic dilators (± placebo): Nulliparous (mm) (Better indicated by higher values)												

1 (Edelman 2006)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	20	20	Not applicable	MD 0.90 higher (0.28 lower to 2.08 higher)	MODERATE	CRITICAL
Baseline cervical dilation - Osmotic dilators + buccal misoprostol (400mcg; 1-3 hours before termination) versus osmotic dilators (± placebo): Parous (mm) (Better indicated by higher values)												
1 (Edelman 2006)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	41	45	Not applicable	MD 0.2 higher (0.56 lower to 0.96 higher)	MODERATE	CRITICAL
Baseline cervical dilation - Osmotic dilators + mifepristone (200mg; 24 hours before termination) versus osmotic dilators: Mixed parity (cm) (Better indicated by higher values)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	98	99	Not applicable	MD 0.2 higher (0.06 to 0.34 higher)	HIGH	CRITICAL
Baseline cervical dilation - Sublingual misoprostol (600mcg; 1.5-2.5 hours before termination) and mifepristone (200mg; 48 hours before termination) versus sublingual misoprostol: Mixed parity (mm) (Better indicated by higher values)												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	Serious[4]	None	221	217	Not applicable	MD 3.7 higher (3.21 to 4.19 higher)	LOW	CRITICAL
Baseline cervical dilation - Vaginal misoprostol (400-600mcg; 1.5-6 hours before termination) and mifepristone (200mg; 4-48 hours before termination) versus vaginal misoprostol (± placebo): Mixed parity (mm) (Better indicated by higher values)												
2 (Carbonell 2007; Casey 2016)	Randomised trials	No serious risk of bias	Very serious[5]	Serious[6]	Serious[4]	None	268	267	Not applicable	Not pooled[4]: Carbonell 2007 MD 4.30 higher (from3.68 higher to 4.92 higher) Casey 2016 MD 0.80 higher (from 0.38 lower to	VERY LOW	CRITICAL

										1.98 higher)		
Cervical trauma (lacerations) - Osmotic dilators + buccal misoprostol (400mcg; 3-4 hours before termination) versus osmotic dilators (± placebo)												
3 (Boraas 2016; Drey 2014; Goldberg 2015)	Randomised trials	No serious risk of bias	Serious[7]	No serious indirectness	Very serious[8]	None	14/211 (6.6%)	12/212 (5.7%)	RR 0.71 (0.13 to 3.96)	10 more per 1000 (from 24 fewer to 82 more)	VERY LOW	CRITICAL
Cervical trauma (lacerations) - Osmotic dilators + mifepristone (200mg; 24 hours before termination) versus osmotic dilators												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	0/99 (0%)	3/99 (3%)	RR 0.14 (0.01 to 2.73)	26 fewer per 1000 (from 30 fewer to 52 more)	LOW	CRITICAL
Cervical trauma (lacerations) - Vaginal misoprostol (400mcg; 4-6 hours before termination) and mifepristone (200mg; 4-6 hours before termination) versus vaginal misoprostol (± placebo)												
1 (Casey 2016)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[9]	None	0/48 (0%)	0/48 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation - Osmotic dilators + buccal misoprostol (400mcg; 3-4 hours before termination) versus osmotic dilators (± placebo)												
2 (Drey 2014; Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	2/196 (1%)	1/197 (0.5%)	RR 1.68 (0.22 to 12.59)	3 more per 1000 (from 4 fewer to 59 more)	LOW	CRITICAL
Uterine perforation - Osmotic dilators + mifepristone (200mg; 24 hours before termination) versus osmotic dilators												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[9]	None	0/98 (0%)	0/99 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation - Vaginal misoprostol (400mcg; 4-6 hours before termination) and mifepristone (200mg; 4-6 hours before termination) versus vaginal misoprostol (± placebo)												
1 (Casey 2016)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[9]	None	0/48 (0%)	0/48 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Pre-operative expulsion - Osmotic dilators and buccal misoprostol (400mcg; 3-4 hours before termination) versus osmotic dilators (± placebo)												
2 (Drey 2014; Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	2/197 (1%)	0/197 (0%)	RR 3 (0.31 to 28.6)	Not estimable	LOW	IMPORTANT

Pre-operative expulsion - Osmotic dilators and mifepristone (200mg; 24 hours before termination) versus osmotic dilators												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[9]	None	0/99 (0%)	0/99 (0%)	Not estimable	Not estimable	MODERATE	IMPORTANT
Pre-operative expulsion - Sublingual misoprostol (600mcg; 1.5-2.5 hours before termination) and mifepristone (200mg; 48 hours before termination) versus sublingual misoprostol												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	No serious imprecision	None	10/225 (4.4%)	1/225 (0.4%)	RR 10 (1.29 to 77.47)	40 more per 1000 (from 1 more to 340 more)	MODERATE	IMPORTANT
Pre-operative expulsion - Vaginal misoprostol (400-600mcg; 1.5-6 hours before termination) and mifepristone (200mg; 4-48 hours before termination) versus vaginal misoprostol (± placebo)												
2 (Carbonell 2007; Casey 2016)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[6]	Serious[4]	None	8/274 (2.9%)	2/273 (0.7%)	RR 3.39 (0.84 to 13.74)	18 more per 1000 (from 1 fewer to 93 more)	LOW	IMPORTANT
Ease of procedure (physician reported) - agree/strongly agree easy to perform - vaginal misoprostol (400mcg; 4-6 hours before termination) and mifepristone (200mg; 4-6 hours before termination) versus vaginal misoprostol (± placebo)												
1 (Casey 2016)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	42/48 (87.5%)	40/47 (85.1%)	RR 1.03 (0.88 to 1.21)	26 more per 1000 (from 102 fewer to 179 more)	HIGH	IMPORTANT
Ease of procedure (physician reported) - rated as (very/extremely) difficult - Osmotic dilators and buccal misoprostol (400mcg; 3-4 hours before termination) versus osmotic dilators (± placebo)												
2 (Drey 2014; Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	23/196 (11.7%)	30/197 (15.2%)	RR 0.77 (0.46 to 1.28)	35 fewer per 1000 (from 82 fewer to 43 more)	LOW	IMPORTANT
Ease of procedure (physician reported) - rated as (very/extremely) difficult - Osmotic dilators and mifepristone (200mg; 24 hours before termination) versus osmotic dilators												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3/98 (3.1%)	15/99 (15.2%)	RR 0.2 (0.06 to 0.68)	121 fewer per 1000 (from 48 fewer to 142 fewer)	HIGH	IMPORTANT
Patient acceptability - rated as satisfied/very satisfied with priming - Osmotic dilators and buccal misoprostol (400mcg; 3 hours before termination) versus osmotic dilators (± placebo)												
2 (Boraas 2016;	Randomised trials	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	90/114 (78.9%)	86/114 (75.4%)	RR 1.05 (0.91 to 1.21)	38 more per 1000 (from 68	HIGH	IMPORTANT

Goldberg 2015)		risk of bias								fewer to 158 more)		
Patient acceptability - rated as satisfied/very satisfied with priming - Osmotic dilators and mifepristone (200mg; 24 hours before termination) versus osmotic dilators												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	80/99 (80.8%)	72/99 (72.7%)	RR 1.11 (0.95 to 1.3)	80 more per 1000 (from 36 fewer to 218 more)	MODERATE	IMPORTANT
Patient acceptability - rated as dissatisfied/very dissatisfied with priming - Osmotic dilators and buccal misoprostol (400mcg; 3 hours before termination) versus osmotic dilators (± placebo)												
2 (Boraas 2016; Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	5/114 (4.4%)	7/114 (6.1%)	RR 0.72 (0.23 to 2.19)	17 fewer per 1000 (from 47 fewer to 73 more)	LOW	IMPORTANT
Patient acceptability - rated as dissatisfied/very dissatisfied with priming - Osmotic dilators and mifepristone (200mg; 24 hours before termination) versus osmotic dilators												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	4/99 (4%)	6/99 (6.1%)	RR 0.67 (0.19 to 2.29)	20 fewer per 1000 (from 49 fewer to 78 more)	LOW	IMPORTANT
Patient acceptability - would choose same method again - vaginal misoprostol (400mcg; 4-6 hours before termination) and mifepristone (200mg; 4-6 hours before termination) versus vaginal misoprostol (± placebo)												
1 (Casey 2016)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	45/48 (93.8%)	44/47 (93.6%)	RR 1 (0.9 to 1.11)	0 fewer per 1000 (from 94 fewer to 103 more)	HIGH	IMPORTANT
Patient acceptability - would recommend to friend - vaginal misoprostol (400mcg; 4-6 hours before termination) and mifepristone (200mg; 4-6 hours before termination) versus vaginal misoprostol (± placebo)												
1 (Casey 2016)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	43/48 (89.6%)	40/47 (85.1%)	RR 1.05 (0.9 to 1.23)	43 more per 1000 (from 85 fewer to 196 more)	HIGH	IMPORTANT
Duration of procedure (minutes; first instrument in to last instrument out) - Osmotic dilators and buccal misoprostol (400mcg; 1-4 hours before termination) versus osmotic dilators (± placebo)												
4 (Boraas 2016; Drey 2014; Edelman	Randomised trials	No serious risk of bias	Serious[10]	Serious[11]	No serious imprecision	None	270	276	Not applicable	MD 0.74 lower (1.97 lower to 0.48 higher)	LOW	IMPORTANT

2006; Goldberg 2015)												
Duration of procedure (minutes; first instrument in to last instrument out) - Osmotic dilators and mifepristone (200mg; 24 hours before termination) versus osmotic dilators												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	98	99	Not applicable	MD 0.74 lower (1.64 lower to 0.16 higher)	HIGH	IMPORTANT
Duration of procedure (minutes; anaesthesia administered to speculum out) - Sublingual misoprostol (600mcg; 1.5-2.5 hours before termination) and mifepristone (200mg; 48 hours before termination) versus sublingual misoprostol												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	No serious imprecision	None	221	217	Not applicable	MD 1.1 lower (2 to 0.2 lower)	MODERATE	IMPORTANT
Duration of procedure (minutes; anaesthesia administered to speculum out) - Vaginal misoprostol (600mcg; 1.5-2.5 hours before termination) and mifepristone (200mg; 48 hours before termination) versus vaginal misoprostol												
2 (Carbonell 2007; Casey 2016)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[6]	No serious imprecision	None	268	267	Not applicable	MD 0.74 lower (1.75 lower to 0.27 higher)	MODERATE	IMPORTANT

CI: confidence interval; mcg: micrograms; MD: mean difference; MID: minimally important difference; RR: relative risk

[1] The quality of evidence was downgraded 2 levels as the 95% confidence interval crosses 2 MIDs

[2] The quality of evidence was downgraded 1 level as the 95% confidence interval crossed 1 MID

[3] The quality of evidence was downgraded 1 level as study includes women with gestational age from 2 weeks lower than population of interest for this question

[4] The quality of evidence was downgraded 2 levels as there were high rates of unexplained heterogeneity (96%) as there was no data for subgroups of interest

[5] The quality of evidence was downgraded 1 level as one study (Carbonell 2007) includes women with gestational age from 2 weeks lower than population of interest for this question

[6] The quality of evidence was downgraded 1 level as study includes women with gestational age from 1 week lower than population of interest for this question

[7] The quality of evidence was downgraded 1 level as there were high rates of unexplained heterogeneity (I squared 59%) as data was not reported for subgroups of interest; direction of effect for Drey 2014 opposite to remaining two studies

[8] Not sufficiently powered to detect this rare outcome; no events of interest

[9] The quality of evidence was downgraded 1 level as there were high rates of unexplained heterogeneity (I squared 61%) as data was not reported for subgroups of interest

[10] The quality of evidence was downgraded 1 level as one study (Edelman 2006) includes women from 1 week lower than population of interest for this question

Table 14: Clinical evidence profile: Comparison 3. Combination A versus combination B

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination A	Combination B	Relative (95% CI)	Absolute	Quality	Importance
Baseline cervical dilation ≥3cm - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + mifepristone (200mg; 24 hours before termination) versus dilators + buccal misoprostol (± placebo)												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	14/27 (51.9%)	12/21 (57.1%)	RR 0.91 (0.54 to 1.52)	51 fewer per 1000 (from 263 fewer to 297 more)	LOW	CRITICAL
Baseline cervical dilation ≥3cm - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + mifepristone (200mg; 24 hours before termination) versus buccal misoprostol + mifepristone												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	14/27 (51.9%)	1/27 (3.7%)	RR 14 (1.98 to 99.13)	481 more per 1000 (from 36 more to 1000 more)	HIGH	CRITICAL
Baseline cervical dilation ≥3cm - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + placebo versus buccal misoprostol + mifepristone (200mg; 24 hours before termination)												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	12/21 (57.1%)	1/27 (3.7%)	RR 15.43 (2.18 to 109.39)	534 more per 1000 (from 44 more to 1000 more)	HIGH	CRITICAL
Baseline cervical dilation (cm) - Dilators + buccal misoprostol (400mcg; 3 hours before termination) versus dilators + mifepristone (200mg; 24 hours before termination) (Better indicated by higher values)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	97	98	Not applicable	MD 0.1 higher (0.1 lower to 0.3 higher)	HIGH	CRITICAL
Cervical trauma (lacerations) - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + mifepristone (200mg; 24 hours before termination) versus buccal misoprostol + mifepristone												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	0/27 (0%)	5/27 (18.5%)	RR 0.09 (0.01 to 1.57)	169 fewer per 1000 (from 183 fewer to 106 more)	LOW	CRITICAL

Cervical trauma (lacerations) - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + mifepristone (200mg; 24 hours before termination) versus dilators + buccal misoprostol (± placebo)												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	0/27 (0%)	1/21 (4.8%)	RR 0.26 (0.01 to 6.12)	35 fewer per 1000 (from 47 fewer to 244 more)	LOW	CRITICAL
Cervical trauma (lacerations) - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + placebo versus buccal misoprostol + mifepristone (200mg; 24 hours before termination)												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/21 (4.8%)	5/27 (18.5%)	RR 0.26 (0.03 to 2.04)	137 fewer per 1000 (from 180 fewer to 193 more)	LOW	CRITICAL
Cervical trauma (lacerations) - Dilators + buccal misoprostol (400mcg; 3 hours before termination) versus dilators + mifepristone (200mg; 24 hours before termination)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	0/100 (0%)	0/99 (0%)	Not estimable	Not estimable	MODERATE	CRITICAL
Uterine perforation - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + mifepristone (200mg; 24 hours before termination) versus dilators + buccal misoprostol (± placebo)												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/27 (3.7%)	0/21 (0%)	RR 2.36 (0.1 to 55.09)	Not estimable	LOW	CRITICAL
Uterine perforation - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + mifepristone (200mg; 24 hours before termination) versus buccal misoprostol + mifepristone												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/27 (3.7%)	2/27 (7.4%)	RR 0.5 (0.05 to 5.19)	37 fewer per 1000 (from 70 fewer to 310 more)	LOW	CRITICAL
Uterine perforation - Dilators + buccal misoprostol (400mcg; 1.5-3 hours before termination) + placebo versus buccal misoprostol + mifepristone (200mg; 24 hours before termination)												
1 (Shaw 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	0/21 (0%)	2/27 (7.4%)	RR 0.25 (0.01 to 5.03)	56 fewer per 1000 (from 73 fewer to 299 more)	LOW	CRITICAL
Uterine perforation - Dilators + buccal misoprostol (400mcg; 3 hours before termination) versus dilators + mifepristone (200mg; 24 hours before termination)												
1 (Goldberg 2015)	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/99 (1%)	0/98 (0%)	RR 2.97 (0.12 to 72.03)	Not estimable	LOW	CRITICAL

		risk of bias										
Pre-operative expulsion - Osmotic dilators + buccal misoprostol (400mcg; 3 hours before termination) versus osmotic dilators + mifepristone (200mg; 24 hours before termination)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/100 (1%)	0/99 (0%)	RR 2.97 (0.12 to 72.05)	Not estimable	LOW	IMPORTANT
Ease of procedure (physician reported) - rated as difficult/very difficult - Osmotic dilators + buccal misoprostol (400mcg; 3 hours before termination) versus osmotic dilators + mifepristone (200mg; 24 hours before termination)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	11/99 (11.1%)	3/98 (3.1%)	RR 3.63 (1.04 to 12.61)	81 more per 1000 (from 1 more to 355 more)	MODERATE	IMPORTANT
Patient acceptability - rated as satisfied/very satisfied with priming - Osmotic dilators + buccal misoprostol (400mcg; 3 hours before termination) versus osmotic dilators + mifepristone (200mg; 24 hours before termination)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	80/100 (80%)	80/99 (80.8%)	RR 0.99 (0.86 to 1.14)	8 fewer per 1000 (from 113 fewer to 113 more)	HIGH	IMPORTANT
Patient acceptability - rated as dissatisfied/very dissatisfied with priming - Osmotic dilators + buccal misoprostol (400mcg; 3 hours before termination) versus osmotic dilators + mifepristone (200mg; 24 hours before termination)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/100 (4%)	4/99 (4%)	RR 0.99 (0.25 to 3.85)	0 fewer per 1000 (from 30 fewer to 115 more)	LOW	IMPORTANT
Duration of procedure (minutes; first instrument in to last instrument out) - Dilators + buccal misoprostol (400mcg; 1.5 hours before termination) + mifepristone (200mg; 24 hours before termination) versus dilators + buccal misoprostol (± placebo)												
1 (Shaw 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	24	21	Not applicable	MD 0.94 higher (2.16 lower to 4.04 higher)	MODERATE	IMPORTANT
Duration of procedure (minutes; first instrument in to last instrument out) - Osmotic dilators + buccal misoprostol (400mcg; 3 hours before termination) versus osmotic dilators + mifepristone (200mg; 24 hours before termination)												
1 (Goldberg 2015)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	98	98	Not applicable	MD 0.75 higher (0.33 lower to 1.83 higher)	HIGH	IMPORTANT

CI: confidence interval; mcg: micrograms; MD: mean difference; MID: minimally important difference; RR: relative risk
[1] The quality of evidence was downgraded 2 levels as the 95% confidence interval crossed 2 MIDs
[2] Not sufficiently powered to detect this rare event; no events of interest
[3] The quality of evidence was downgraded 1 level as the 95% confidence interval crossed 1 MID

Table 15: Clinical evidence profile: Comparison 4. Overnight osmotic dilators versus same-day osmotic dilators

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Overnight dilators**	**Same-day dilators**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Baseline cervical dilation (mm) (Better indicated by higher values)												
1 (Newmann 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35	34	Not applicable	MD 11.7 higher (6.66 to 16.74 higher)	HIGH	CRITICAL
Cervical trauma (lacerations)												
1 (Newmann 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/35 (2.9%)	0/34 (0%)	RR 2.92 (0.12 to 69.2)	Not estimable	LOW	CRITICAL
Ease of procedure (physician reported) - inadequate dilation												
1 (Newmann 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	7/30 (23.3%)	19/32 (59.4%)	RR 0.39 (0.19 to 0.8)	362 fewer per 1000 (from 119 fewer to 481 fewer)	HIGH	CRITICAL
Patient acceptability - Satisfied with termination												
1 (Newmann 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	24/33 (72.7%)	26/34 (76.5%)	RR 0.95 (0.72 to 1.26)	38 fewer per 1000 (from 214 fewer to 199 more)	LOW	IMPORTANT
Patient acceptability - Satisfied with overall clinic experience												
1 (Newmann 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	22/33 (66.7%)	25/34 (73.5%)	RR 0.91 (0.66 to 1.24)	66 fewer per 1000 (from 250 fewer to 176 more)	MODERATE	IMPORTANT

Duration of procedure (minutes; first instrument in to last instrument out) - Mixed parity												
1 (Newmann 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	35	34	Not applicable	MD 2.2 lower (4.28 to 0.12 lower)	MODERATE	IMPORTANT
Duration of procedure (minutes; first instrument in to last instrument out) - Nulliparous												
1 (Newmann 2014)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	12	9	Not applicable	MD 5 lower (10.53 lower to 0.53 higher)	MODERATE	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: relative risk
[1] The quality of evidence was downgraded 2 levels as the 95% confidence interval crosses 2 MIDs
[2] The quality of evidence was downgraded 1 level as the 95% confidence interval crosses 1 MID

Table 16: Clinical evidence profile: Comparison 5. Sublingual misoprostol versus vaginal misoprostol (both 600mcg misoprostol 1.5-2.5 hours before termination; 200mg 28 hours before termination)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Misoprostol route A (sublingual)**	**Misoprostol route B (vaginal)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Baseline cervical dilation (mm) - Misoprostol + mifepristone (Better indicated by higher values)												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	221	220	Not applicable	MD 0.2 higher (0.32 lower to 0.72 higher)	MODERATE	CRITICAL
Baseline cervical dilation (mm) - Misoprostol only (Better indicated by higher values)												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	217	219	Not applicable	MD 0.8 higher (0.21 to 1.39 higher)	MODERATE	CRITICAL
Pre-operative expulsion - Misoprostol + mifepristone												
1 (Carbonell 2007)	Randomised trials	No serious	No serious inconsistency	Serious[1]	Very serious[2]	None	10/225 (4.4%)	7/225 (3.1%)	RR 1.43 (0.55 to 3.69)	13 more per 1000 (from 14	VERY LOW	IMPORTANT

		risk of bias								fewer to 84 more)		
Pre-operative expulsion - Misoprostol only												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	Very serious[2]	None	1/225 (0.44%)	2/225 (0.89%)	RR 0.5 (0.05 to 5.47)	4 fewer per 1000 (from 8 fewer to 40 more)	VERY LOW	IMPORTANT
Duration of procedure (minutes; anaesthesia administered to speculum out) - Misoprostol + mifepristone												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	221	220	Not applicable	MD 0.4 lower (1.27 lower to 0.47 higher)	MODERATE	IMPORTANT
Duration of procedure (minutes; anaesthesia administered to speculum out) - Misoprostol only												
1 (Carbonell 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	217	219	Not applicable	MD 0 higher (1.08 lower to 1.08 higher)	MODERATE	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: relative risk

[1] The quality of evidence was downgraded 1 level as study includes women with gestational age from 1 week lower than population of interest for this question

[2] The quality of evidence was downgraded 2 levels as 95% confidence interval crosses 2 MIDs

Appendix G – Economic evidence study selection

Economic evidence for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

No economic evidence was identified which was applicable to this review question.

Economic evidence for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

No economic evidence was identified which was applicable to this review question.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

No economic evidence was identified which was applicable to this review question.

Economic evidence tables for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

No economic evidence was identified which was applicable to this review question.

Economic evidence profiles for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

No economic analysis was conducted for this review question.

Economic analysis for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

Excluded studies for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

Clinical studies

Study	Reason for Exclusion
Anonymous, Cervical ripening with mifepristone (RU 486) in late first trimester abortion. World Health Organization Task Force on Postovulatory Methods of Fertility Regulation, Contraception, 50, 461-75, 1994	Pre-2000
Aronsson, A., Fiala, C., Stephansson, O., Granath, F., Watzer, B., Schweer, H., Gemzell-Danielsson, K., Pharmacokinetic profiles up to 12 h after administration of vaginal, sublingual and slow-release oral misoprostol, Human Reproduction, 22, 1912-8, 2007	Outcomes not in PICO: only pharmacokinetic measures
Aronsson, A., Helstrom, L., Gemzell-Danielsson, K., Sublingual compared with oral misoprostol for cervical dilatation prior to vacuum aspiration: A randomized comparison, Contraception, 69, 165-169, 2004	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Aronsson, A., Ulfgren, A. K., Stabi, B., Stavreus-Evers, A., Gemzell-Danielsson, K., The effect of orally and vaginally administered misoprostol on inflammatory mediators and cervical ripening during early pregnancy, Contraception, 72, 33-9, 2005	Outcomes not in PICO: immunohistochemical
Ashok, P. W., Hamoda, H., Nathani, F., Flett, G. M., Templeton, A., Randomised controlled study comparing oral and vaginal misoprostol for cervical priming prior to surgical termination of pregnancy, 110, 1057-61, 2003	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Bartz,D., Maurer,R., Allen,R.H., Fortin,J., Kuang,B., Goldberg,A.B., Buccal misoprostol compared with synthetic osmotic cervical dilator before surgical abortion: a randomized controlled trial, Obstetrics and Gynecology, 122, 57-63, 2013	Overlaps gestational boundaries between questions 2.6 and 2.7: similar number of weeks under each question so unable to reliably inform practice for either group
Bokstrom, H., Wiqvist, N., Preoperative dilatation of the cervix at legal abortion with a synthetic, fast-swelling hygroscopic tent, Acta obstetricia ET gynecologica scandinavica, 68, 313-8, 1989	Non-randomised study

Study	Reason for Exclusion
Bugalho, A., Bique, C., Almeida, L., Bergstrom, S., Application of vaginal misoprostol before cervical dilatation to facilitate first-trimester pregnancy interruption, Obstetrics & GynecologyObstet Gynecol, 83, 729-31, 1994	Pre-2000
Burnett, M. A., Corbett, C. A., Gertenstein, R. J., A randomized trial of laminaria tents versus vaginal misoprostol for cervical ripening in first trimester surgical abortion, Journal of Obstetrics & Gynaecology Canada: JOGCJ Obstet Gynaecol Can, 27, 38-42, 2005	Overlaps gestational boundaries between questions 2.6 and 2.7: greater number of weeks under question 2.6 but osmotic dilators not of interest for this group
Cahill, E., Henkel, A., Shaw, J., Blumenthal, P. D., Shaw, K. A., Adjunctive misoprostol for late second trimester D&E: A systematic review and meta-analysis, International Journal of Gynecology and Obstetrics, 143 (Supplement 3), 818, 2018	Conference abstract - insufficient presentation of results
Caliskan, E., Filiz, T., Yucesoy, G., Coskun, E., Vural, B., Corakci, A., Sublingual versus vaginal misoprostol for cervical ripening PRIOR TO manual vacuum aspiration under local anaesthesia: a randomized study, European journal of contraception & reproductive health care, 12, 372-7, 2007	Comparison not in PICO (Route, dose and interval differ between arms)
Carbonell, J. L., Velazco, A., Rodriguez, Y., Tanda, R., Sanchez, C., Barambio, S., Valera, L., Chami, S., Valero, F., Aragon, S., Mari, J., Oral versus vaginal misoprostol for cervical priming in first-trimester abortion: a randomized trial, The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception, 6, 134-140, 2001	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Casey, F. E., Wegelin, J., Reeves, M., Twenty-four hour mifepristone combined with vaginal versus buccal misoprostol prior to d&e, Obstetrics and Gynecology, 131 (Supplement 1), 76S, 2018	Conference abstract - insufficient presentation of results
Cohn, M., Stewart, P., Pretreatment of the primigravid uterine cervix with mifepristone 30 h prior to termination of pregnancy: a double blind study, British Journal of Obstetrics & GynaecologyBr J Obstet Gynaecol, 98, 778-82, 1991	Pre-2000
Costescu, D., Guilbert, E., No. 360-Induced Abortion: Surgical Abortion and Second Trimester Medical Methods, Journal of Obstetrics and Gynaecology Canada, 40, 750-783, 2018	Clinical guideline
Creinin, M. D., Mifepristone vs. osmotic dilator insertion for cervical preparation prior to surgical	Letter

Study	Reason for Exclusion
abortion at 14-16 weeks: A randomized trial, Contraception, 87, 507-508, 2013	
Creinin, M. D., Hern, W. M., Laminaria versus Dilapan osmotic cervical dilators for second-trimester abortion [10], American journal of obstetrics and gynecology, 173, 354-355, 1995	Letter
Darney, P. D., Dorward, K., Cervical dilation before first-trimester elective abortion: A controlled comparison of meteneprost, laminaria, and hypan, Obstetrics and gynecology, 70, 397-400, 1987	Outcomes not in PICO
Dean, G., Colarossi, L., Porsch, L., Balakumar, K., Dayananda, I., Misoprostol dose and timing before surgical abortion at 13 to 16 weeks gestation: A randomized trial, Contraception, 96 (4), 264, 2017	Dose and interval differ between arms
Dey, M., Oral misoprostol is an effective and acceptable alternative to vaginal administration for cervical priming before first trimester pregnancy termination, Medical Journal Armed Forces India, 69, 27-30, 2013	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Durlot, F., Dubois, C., Brunerie, J., Frydman, R., Efficacy of progesterone antagonist RU486 (Mifepristone) for pre-operative cervical dilatation during first trimester abortion, Human Reproduction, 3, 583-584, 1988	Pre-2000
Ercan, C. M., Coksuer, H., Karasahin, K. E., Alanbay, I., Aydogan, U., Parlak, A., Baser, I., Comparison of different preoperative sublingual misoprostol regimens for surgical termination of first trimester pregnancies: a prospective randomized trial, Journal of reproductive medicine, 56, 247-53, 2011	Indirect population: 30% fetal demise; results not presented separately for population in PICO
Fiala, C., Aronsson, A., Stephansson, O., Gemzell-Danielsson, K., Effects of slow release misoprostol on uterine contractility in early pregnancy, Human Reproduction, 20, 2648-52, 2005	Outcomes not in PICO or insufficiently reported
Ficicioglu, C., Tasdemir, M., Tasdemir, S., Effect of vaginal misoprostol application for cervical softening in pregnancy interruption before ten weeks of gestation, Acta obstetricia ET gynecologica scandinavica, 75, 54-6, 1996	Pre-2000
Fong,Y.F., Singh,K., Prasad,R.N., A comparative study using two dose regimens (200 microg or 400 microg) of vaginal misoprostol for pre-operative cervical dilatation in first trimester nulliparae, British Journal of Obstetrics and Gynaecology, 105, 413-417, 1998	Pre-2000

Study	Reason for Exclusion
Ganer Herman, H., Kerner, R., Gluck, O., Feit, H., Keidar, R., Bar, J., Sagiv, R., Different routes of misoprostol for cervical priming in first trimester surgical abortions: a randomized blind trial, Archives of Gynecology & ObstetricsArch Gynecol Obstet, 295, 943-950, 2017	Indirect population: 26% undergoing procedure for incomplete miscarriage; results not reported separately for population in PICO
Gilliam, M. L., Cervical preparation for first trimester surgical abortion, Obstetrics and gynecology, 115, 1075-1076, 2010	Abstract >2 years old
Grandi, P, Giudici, G, Oral administration of an antiprogesterone (Mifepristone, RU 486) for preparing the cervix uteri for pregnancy interruption during the first trimester, Journal de gynecologie, obstetrique ET biologie de la reproduction, 18, 801-808, 1989	Non-English language
Guo, Q., Qian, Z., Huang, L., Two cervical preparation regimens prior to surgical abortion at 10-14 weeks of gestation: A randomized clinical trial, Journal of Maternal-Fetal and Neonatal Medicine, 30, 2686-2689, 2017	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Gupta, J. K., Johnson, N., Should we use prostaglandins, tents or progesterone antagonists for cervical ripening before first trimester abortion?, Contraception, 46, 489-497, 1992	Non-randomised study
Gupta,J.K., Johnson,N., Effect of mifepristone on dilatation of the pregnant and non-pregnant cervix, Lancet, 335, 1238-1240, 1990	Insufficient presentation of results
Hamoda, H., Ashok, P. W., Flett, G. M., Templeton, A., A randomized controlled comparison of sublingual and vaginal administration of misoprostol for cervical priming before first-trimester surgical abortion, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 190, 55-9, 2004	Insufficient presentation of results
Heidvall, K., Radestad, A., Christensen, N. J., Lindgren, J. A., Production of 12-hydroxyeicosatetraenoic acid in early pregnant uterine cervix--lack of correlation to mifepristone-induced cervical ripening. A double-blind randomized biomechanical and biochemical study, Prostaglandins, 43, 473-82, 1992	Pre-2000
Hern, W. M., Laminaria versus Dilapan osmotic cervical dilators for outpatient dilation and evacuation abortion: randomized cohort comparison of 1001 patients, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 171, 1324-8, 1994	Comparison inconsistent with protocol – laminaria versus dilapan
Hern, W. M., Cervical treatment with Dilapan prior to second trimester dilation and evacuation abortion: a pilot study of 64 patients, The	Non-randomised study

Study	Reason for Exclusion
American Journal of Gynecologic HealthAm J Gynecol Health, 7, 23-6, 1993	
Jensen, Nm, Burgaard, P, Petersen, Hd, Cervical dilatation with Lamicel in gravida I women applying for termination of pregnancy, Ugeskrift for laeger, 151, 1672-1674, 1989	Non-English language
Kapp, N., Whyte, P., Tang, J., Jackson, E., Brahmi, D., A review of evidence for safe abortion care, Contraception, 88, 350-63, 2013	Comparisons not in PICO - no new studies identified
Kapp, Nathalie, Lohr, Patricia A, Ngo, Thoai D, Hayes, Jennifer L, Cervical preparation for first trimester surgical abortion, Cochrane Database of Systematic Reviews, 2010	Comparisons and outcomes not in PICO
Lawrie,A., Penney,G., Templeton,A., A randomised comparison of oral and vaginal misoprostol for cervical priming before suction termination of pregnancy, British Journal of Obstetrics and Gynaecology, 103, 1117-1119, 1996	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Lefebvre, Y., Proulx, L., Elie, R., Poulin, O., Lanza, E., The effects of RU-38486 on cervical ripening. Clinical studies, American journal of obstetrics and gynecology, 162, 61-65, 1990	Insufficient presentation of results
MacIsaac, L., Grossman, D., Balistreri, E., Darney, P., A randomized controlled trial of laminaria, oral misoprostol, and vaginal misoprostol before abortion, Obstetrics & GynecologyObstet Gynecol, 93, 766-70, 1999	Pre-2000
Madrigal, J. M., Aparicio, J., Patel, A., First trimester surgical abortion pain using buccal misoprostol and/or lidocaine paracervical block, International Journal of Gynecology and Obstetrics, 143 (Supplement 3), 374, 2018	Conference abstract - insufficient presentation of results
Mirteimouri, M., Bakhtiarizadeh, T., Hadavi, F., Comparison of cervical ripening with and without nitroglycerin before first trimester abortion, Iranian journal of obstetrics, gynecology and infertility, 21, 1â5, 2018	Non-English language
Morris, N. D., McCallum, G. I., Hammond, L., Preoperative cervical dilatation: A trial of laminaria tents and prostaglandin F(2alpha) gel, Australian and New Zealand Journal of Obstetrics and Gynaecology, 26, 36-39, 1986	Insufficient presentation of results
Nath, J., Jain, M., Najam, R., Sharma, R., To compare the Effectiveness and Tolerability of Misoprostol as a Cervical Ripening Agent in the First Trimester Abortion through Sublingual and Vaginal Routes of Administration, Bangladesh journal of obstetrics and gynecology, 27, 63-66, 2012	Outcomes not in PICO

Study	Reason for Exclusion
Newmann, Sara J, Dalve-Endres, Andrea, Diedrich, Justin T, Steinauer, Jody E, Meckstroth, Karen, Drey, Eleanor A, Cervical preparation for second trimester dilation and evacuation, Cochrane Database of Systematic Reviews, 2010	Comparisons and outcomes not in PICO
Ngai, S. W., Chan, Y. M., Tang, O. S., Ho, P. C., The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: A randomized trial, Human Reproduction, 14, 2139-2142, 1999	Pre-2000
Ngai, S. W., Yeung, K. C., Lao, T., Ho, P. C., Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomised study, British Journal of Obstetrics & GynaecologyBr J Obstet Gynaecol, 103, 1120-3, 1996	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Ngai,S.W., Tang,O.S., Lao,T., Ho,P.C., Ma,H.K., Oral misoprostol versus placebo for cervical dilatation before vacuum aspiration in first trimester pregnancy, Human Reproduction, 10, 1220-1222, 1995	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Ohannessian, A., Baumstarck, K., Maruani, J., Cohen-Solal, E., Auquier, P., Agostini, A., Mifepristone and misoprostol for cervical ripening in surgical abortion between 12 and 14 weeks of gestation: a randomized controlled trial, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 201, 151-5, 2016	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Okanlomo,K.A., Ngotho,D., Moodley,J., Effect of misoprostol for cervical ripening prior to pregnancy interruption before twelve weeks of gestation, East African Medical Journal, 76, 552-555, 1999	Outcomes not in PICO
Oppegaard, K. S., Qvigstad, E., Nesheim, B. I., Oral versus self-administered vaginal misoprostol at home before surgical termination of pregnancy: A randomised controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 58-64, 2006	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Oppegaard,K.S., Abdelnoor,M., Nesheim,B.I., Jerve,F., Eskild,A., The use of oral misoprostol for pre-abortion cervical priming: a randomised controlled trial of 400 versus 200 microg in first trimester pregnancies, BJOG : an international journal of obstetrics and gynaecology, 111, 154-159, 2004	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Parveen, S., Khateeb, Z. A., Mufti, S. M., Shah, M. A., Tandon, V. R., Hakak, S., Singh, Z., Yasmeen, S., Mir, S. A., Tabasum, R., Jan, N.,	Population not in PICO: incomplete/missed abortion

Study	Reason for Exclusion
Comparison of sublingual, vaginal, and oral misoprostol in cervical ripening for first trimester abortion, Indian journal of pharmacology, 43, 172-5, 2011	
Platz-Christensen, J. J., Nielsen, S., Hamberger, L., Is misoprostol the drug of choice for induced cervical ripening in early pregnancy termination?, Acta obstetricia ET gynecologica scandinavica, 74, 809-12, 1995	Trial 1 and 2 comparisons not in PICO. Trial 3 has insufficient presentation of results
Prairie,B.A., Lauria,M.R., Kapp,N., Mackenzie,T., Baker,E.R., George,K.E., Mifepristone versus laminaria: a randomized controlled trial of cervical ripening in midtrimester termination, Contraception, 76, 383-388, 2007	Population not in PICO (not scheduled for surgical termination)
Punjyashthira, A., Pongrojpaw, D., Suwannarurk, K., Bhamarapravatana, K., The effectiveness of sublingual or oral administration of misoprostol for cervical ripening before manual vacuum aspiration in first trimester termination of pregnancy: randomized controlled trial, Journal of the Medical Association of Thailand, 97, 1009-15, 2014	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Rabe, T, Basse, H, Thuro, H, Kiesel, L, Runnebaum, B, Effect of the PGE1 methyl analog misoprostol on the pregnant uterus in the first trimester, Geburtshilfe und frauenheilkunde, 47, 324-331, 1987	Non-English language
Radestad, A., Christensen, N. J., Stromberg, L., Induced cervical ripening with mifepristone in first trimester abortion. A double-blind randomized biomechanical study, Contraception, 38, 301-312, 1988	Pre-2000
Radestad, A., Thyberg, J., Christensen, N. J., Cervical ripening with mifepristone (RU 486) in first trimester abortion. An electron microscope study, Human Reproduction, 8, 1136-1142, 1993	Outcomes not in PICO: structural changes in the cervix
Radulovic, N. V., Ekerhovd, E., Abrahamsson, G., Norstrom, A., Cervical priming in the first trimester: morphological and biochemical effects of misoprostol and isosorbide mononitrate, Acta obstetricia ET gynecologica scandinavica, 88, 43-51, 2009	Insufficient presentation of results
Saxena, P., Salhan, S., Sarda, N., Comparison between the sublingual and oral route of misoprostol for pre-abortion cervical priming in first trimester abortions, Human Reproduction, 19, 77-80, 2004	Comparison with oral misoprostol - not included by Guideline Committee due to slower absorption and greater side effects
Schaub, B, Fuhrer, P, Sainte, Rd, Intravaginal misoprostol before first trimester induced	Non-English language

Study	Reason for Exclusion
abortion in nulliparous women, Contraception fertilite sexualite, 24, 67-71, 1996	
Schaub, B, Fuhrer, P, Sainte-Rose, D, Intravaginal misoprostol before induced abortion in nulliparous women, Contraception, fertilite, sexualite (1992), 24, 67-71, 1996	Non-English language
Scheepers, H. C. J., Van Erp, E. J. M., Van Den Bergh, A. S., Use of misoprostol in first and second trimester abortion: A review, Obstetrical and Gynecological Survey, 54, 592-600, 1999	Comparisons not in PICO
Shetty, J., Chawla, R., Pandey, D., Kamath, A., Guddattu, V., Sublingual misoprostol: a better choice for cervical priming before manual vacuum aspiration, Indian journal of medical sciences, 64, 356-62, 2010	Comparison not in PICO: Route and interval differ between arms
Singh, K., Fong, Y. F., Prasad, R. N., Dong, F., Evacuation interval after vaginal misoprostol for preabortion cervical priming: a randomized trial, Obstetrics & Gynecology, 94, 431-4, 1999	Comparison not in PICO: Dose and interval differ between arms
Singh, K., Fong, Y. F., Prasad, R. N., Dong, F., Randomized trial to determine optimal dose of vaginal misoprostol for preabortion cervical priming, Obstetrics & Gynecology, 92, 795-8, 1998	Pre-2000
Singh, K., Fong, Y. F., Prasad, R. N., Dong, F., Vaginal misoprostol for pre-abortion cervical priming: is there an optimal evacuation time interval?, British Journal of Obstetrics & Gynaecology, 106, 266-9, 1999	Comparison not in PICO: Dose and interval differ between arms
Suchati, Chiawchanchaiaratana, Pavit, Sutchritpongsa, Dittakarn, Boriboonhirunsarn, Effectiveness of vaginal misoprostol application for cervical priming in first-trimester pregnancy termination: a randomized clinical trial, Thai journal of obstetrics and gynaecology, 15, 145-151, 2003	Surgical method for termination of pregnancy not in PICO: sharp curettage
Tang, O. S., Schweer, H., Lee, S. W., Ho, P. C., Pharmacokinetics of repeated doses of misoprostol, Human Reproduction, 24, 1862-9, 2009	Unclear whether intention is medical ToP or surgical ToP but the misoprostol dose appears inappropriate for cervical priming
Urquhart, D. R., Templeton, A. A., Mifepristone (RU 486) for cervical priming prior to surgically induced abortion in the late first trimester, Contraception, 42, 191-199, 1990	Pre-2000
Wang, Y. X., Zeng, R., Huang, M. J., Zhu, W. J., Tu, M., Comparison of Preliminary Clinical Efficacy for Two Cervical Preparations for Early Second-trimester Pregnancy Termination at 12-17 Weeks gestation, Journal of reproduction and contraception, 22, 83-88, 2011	Population not in PICO: Medical termination of pregnancy

Study	Reason for Exclusion
Wiebe, E. R., Rawling, M. J., Vaginal misoprostol before first trimester abortion, International Journal of Gynecology and Obstetrics, 60, 175-176, 1998	Insufficient presentation of methods and results

PICO: population, intervention, comparison and outcomes; ToP: termination of pregnancy
Literature search and study selection undertaken for review question 2.6 and review question 2.7 simultaneously

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal regimen for cervical priming (including no cervical priming as an option) before surgical termination of pregnancy up to and including 13^{+6} weeks' gestation

No research recommendations were made for this review question.

Research recommendations for review question: What is the optimal regimen for cervical priming before surgical termination of pregnancy between 14^{+0} and 24^{+0} weeks' gestation?

What are the most effective and acceptable methods of cervical priming before dilatation and evacuation after 16^{+0} weeks' gestation?

Why this is important?

Adequate cervical preparation is essential to the safe conduct of D&E. Osmotic dilators inserted into the cervix 24 to 48 hours before a uterine evacuation are effective but their use requires an additional clinic visit, skilled staff, and an uncomfortable procedure. These characteristics negatively impact the acceptability of osmotic dilators to women and may present a barrier to their use in some settings. Pharmacologic agents, such as mifepristone and misoprostol, could reduce the discomfort associated with osmotic dilator use, increase convenience, and lower costs to women and services. Osmotic dilators inserted into the cervix on the same day as the evacuation may be sufficiently effective while reducing the costs, and total duration of treatment incurred with preparatory regimens over 1 or more days.

Table 17: Research recommendation rationale

Research question	What are the most effective and acceptable methods of cervical priming before dilatation and evacuation after 16^{+0} weeks' gestation?
Importance to 'patients' or the population	Osmotic dilators inserted into the cervix 24 to 48 hours before a surgical evacuation are effective, but this intervention requires an additional clinic visit, skilled personnel, and an uncomfortable procedure. Pharmacologic priming agents have been studied as an alternative to osmotic dilators and appear to be more acceptable to women. However, comparative data are insufficient to recommend them as a replacement for osmotic dilators as gestational age advances beyond 16^{+0} to 19^{+0} weeks. Cervical preparation using osmotic dilators on the same day as surgical evacuation would be preferred by women over current regimens used over 2 or more days if it is as effective as treatment.
Relevance to NICE guidance	The guideline development group was asked to identify optimal regimens for cervical priming before surgical termination of pregnancy between 14^{+0} and 23^{+6} weeks' gestation. While there was sufficient evidence to support a routine offer of osmotic dilators, the committee were unsure if the benefits of inserting osmotic dilators the day before the termination, compared with the same-day, would outweigh the negative impact this may have on women and services as it would require additional travel or time off and possibly an overnight stay away from home. There was also evidence of lower patient acceptability with this method of cervical preparation than with pharmacologic agents. The committee recommended that mifepristone or misoprostol are

Research question	What are the most effective and acceptable methods of cervical priming before dilatation and evacuation after 16^{+0} weeks' gestation?
	considered as alternatives when osmotic dilators are contraindicated or declined but acknowledged that the evidence for pharmacologic agents was limited and could only make recommendations up to 16^{+0} to 19^{+0} weeks of gestation, depending on the agent used.
Relevance to the NHS	Most terminations performed after 14^{+0} weeks of gestation in Britain are undertaken by D&E. Identifying effective and acceptable methods for cervical preparation is essential to successful delivery of safe D&E within the NHS and in services commissioned by the NHS. Reducing the need for an additional clinic visit for insertion of osmotic dilators could reduce costs and barriers to the delivery of surgical methods of termination in the second trimester.
National priorities	Access to a choice of safe and acceptable methods of termination at all gestations allowable by law is a public health priority.
Current evidence base	There is no evidence on the effectiveness of mifepristone alone after 16^{+0} weeks of gestation or for misoprostol alone compared with osmotic dilators after 19^{+0} weeks' gestation; therefore, it was not possible to recommend an alternative to osmotic dilators from 19^{+1} weeks' gestation as effectiveness is not known. There was very limited evidence for the efficacy of mifepristone given 24 hours prior to termination in combination with misoprostol compared with other cervical priming regimens. There is also insufficient evidence to recommend a specific misoprostol regimen to use alone up to 19^{+0} weeks of gestation. One RCT study found that insertion of laminaria the day prior to a surgical evacuation at 13^{+6} to 17^{+6} weeks of gestation resulted in better baseline cervical dilation and procedure ease compared to synthetic dilators inserted 4 to 6 hours before evacuation. However, there were no significant differences in a number of other outcomes such as safety, acceptability or procedure duration. There is no evidence comparing overnight to same day dilators over 18^{+0} weeks of gestation. One RCT reported on outcomes with same day synthetic dilators alone or with adjunctive misoprostol from 16^{+0} to 20^{+6} weeks of gestation. The project was stopped early on safety grounds and so had insufficient statistical power to detect differences in their primary outcome (procedure duration) or apparent differences in adverse events by gestation age or as a result of the use of adjunctive misoprostol.
Equality	N/A

D&E: dilatation and evacuation; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; N/A: not applicable; RCT: randomised controlled trial

Table 18: Research recommendation modified PICO table

Criterion	Explanation
Population	Women seeking surgical termination between 16^{+0} and 23^{+6} weeks of gestation
Intervention	Synthetic osmotic dilators inserted 3 to 6 hours prior to evacuation, with and without adjunctive misoprostol Mifepristone alone Misoprostol alone Mifepristone and misoprostol
Comparator	Overnight osmotic dilators
Outcome	• Baseline cervical dilation

Criterion	Explanation
	• Incidence of cervical laceration • Incidence of uterine perforation • Incidence of extramural delivery • Subjective ease of evacuation • Patient acceptability/preference • Procedure duration • Need for additional procedure
Study design	Randomised controlled trial
Timeframe	2 years
Additional information	Depending on the scale of any proposed trial and likely number of participants, several trials with fewer comparators (e.g. pharmacological versus standard management of overnight dilators, or same day dilators with or without misoprostol versus standard management) could be conducted separately. Limited evidence suggests that the combination of mifepristone and misoprostol may be effective for cervical preparation before D&E, however, an interval of 48 hours between medications has been associated with an unacceptably high rate of extramural deliveries which are distressing for staff and women. In addition, women prefer prompt access to treatment and lengthy intervals between medication administration and initiation of the procedure prolongs the total treatment duration. Identifying the optimal interval between mifepristone and misoprostol that balances achieving adequate cervical dilation while avoiding risks of extramural delivery would be a useful contributor to studies of this regimen. There is insufficient evidence to recommend a specific dose, route or timing of misoprostol for cervical priming before D&E.

D&E: dilatation and evacuation